

ABSTRACT OF THESIS

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Degree..... Doctor of Philosophy Date..... April 1964

Title of Thesis..... Synthetic and Mechanistic Studies in

..... Carbohydrate Chemistry

The aim of the work described in this thesis was to synthesise a sugar having the ring oxygen replaced by sulphur. 5-Deoxy-5-thio-D-xylopyranose and a number of its derivatives were successfully synthesised. This led to the study of the reactivity of these compounds and their oxygen analogues in some typical carbohydrate reactions. The results of these experiments provided further evidence concerning the mechanisms of certain carbohydrate reactions.

Part I : A discussion of the physical and chemical properties of analogous oxygen and sulphur compounds. This discussion was of interest in connection with the comparison of the reactivity of sulphur sugars and their oxygen analogues, and particularly, because a comprehensive survey of this type is not available in the literature.

Part II : 5-Deoxy-5-thio-D-xylopyranose and its derivatives. Section I of this part described the preparation and properties of 5-deoxy-5-thio-D-xylopyranose. Evidence, based on UV and IR spectroscopy, N.M.R. studies, chemical reactions, and mutarotation studies, is presented as proof of the existence of the sulphur ring. The mutarotation reaction of 5-deoxy-5-thio-D-xylopyranose and its oxygen analogue was carried out in two buffered solutions of different pH and the results compared. The production of 2-thiophen-aldehyde and 2-furfuraldehyde from 5-deoxy-5-thio-D-xylopyranose and its oxygen analogue respectively was studied.

Section II describes the preparation, reactions, and methanolysis of 2,3,4-tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranosyl 1-bromide. The reactions included the Koenigs-Knorr reaction and the reaction of the acetobromide with silver acetate. The results of the methanolysis of the sulphur sugar acetohalide and its oxygen analogue were in agreement with the accepted unimolecular mechanism, and the fact that the oxygen-ring sugar reacts forty times faster than its sulphur analogue is satisfactorarily explained.

Section III describes the preparation and hydrolysis of methyl 5-deoxy-5-thio- α - and β -D-xylopyranosides. The kinetic results of the hydrolyses of these methyl glycosides and of methyl β -D-xylopyranoside enabled us to lend support to one of two proposed mechanisms for the acid hydrolysis of glycosides.

The final section consists of a brief review of the work, on sugars with sulphur in the ring, carried out in other laboratories, since the beginning of the present study.

Part III : Experimental. This consists of a detailed description of the synthetic and kinetic experiments, etc., discussed in Part II.

SYNTHETIC AND MECHANISTIC STUDIES IN

CARBOHYDRATE CHEMISTRY

by

KERR CARMICHAEL YULE, A.H.-W.C.

Thesis presented for the Degree of Doctor of Philosophy of
the University of Edinburgh in the Faculty of Science.

April 1964



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ACKNOWLEDGMENTS

It is a pleasure to have this opportunity of expressing my gratitude to Dr. J.C.P. Schwarz for his help, guidance and encouragement during these past three years of research.

I also wish to thank Professor E.L. Hirst, C.B.E., F.R.S., for his interest in the work and for the provision of laboratory facilities, and the Department of Scientific and Industrial Research for a maintainance grant. Thanks are also due to Dr. John Knox of this Department, for advice concerning the design and operation of a Gas-Liquid Chromatography apparatus and Ewen Collins, B.Sc. for help with some of the experimental work.

Last, but not least, I wish to congratulate my wife Ann on surviving my vagaries of mood, and also thank her for typing this thesis.

Perhaps my feelings towards the end of this period of research can best be expressed by the following quotation from The Wife of Usher's Well :

The cock doth craw, the day doth daw,
The channerin worm doth chide....

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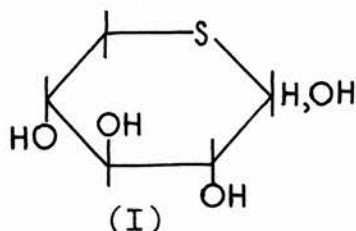
INTRODUCTION

Since oxygen and sulphur are in the same group of the periodic table and hence possess analogous outer valence shells, it is no surprise that there are many sulphur analogues of oxygen containing organic compounds, including sugars. Although the number of sugars containing sulphur in place of oxygen is comparatively small, it is interesting to note that the first example of a thiosugar was observed ⁽¹⁾ as long ago as 1831, when the glycoside sinalbin, was isolated from the mustard oil glucosides. Sinalbin is a glycoside of 1- thioglucose i.e. the O₍₁₎ of glucose is replaced by S. The chemistry of 1- thioglucose was investigated ⁽²⁾ in detail at the beginning of this century and more recently sugar derivatives in which S replaces O in other positions (e.g. positions 2, 3 and 6) have been prepared ⁽³⁾.

However, when the present work was begun, no derivative in which the ring oxygen is replaced by sulphur was known. The aim of our work, then, was to see if sugar derivatives with sulphur in the ring could in fact be synthesised, and to see whether a comparison of their reactivity with that of the corresponding oxygen compounds, would throw any light on the mechanisms of carbohydrate reactions.

It was decided to attempt the preparation of 5-deoxy-5-thio-D-xylopyranose [#] (I), since replacement reactions

on C₍₅₎ of a pentofuranose are readily carried out. The preparation of a 5-deoxy-5-thio-hexopyranose would require a replacement at C₍₅₎ in a hexose derivative; such replacements generally proceed less smoothly.



Note : In the original publication⁽⁴⁾, 5-deoxy-5-thio-D-xylopyranose (I) was referred to as D-xyllothiapyranose, but, since then, both Chemical Abstracts and the Chemical Society have recommended the use of the above nomenclature.

The synthesis of 5-deoxy-5-thio-D-xylopyranose and a number of its derivatives was eventually achieved and this work is described in detail in Part II together with the syntheses of other sugars with sulphur in the ring, recently carried out in other laboratories.

Since the chemistry of thiosugars has recently been reviewed in detail⁽⁵⁾, this will not be attempted here. However, in connection with the comparison of the reactivity of sulphur sugars and their oxygen analogues, a discussion of the physical and chemical properties of analogous oxygen and sulphur compounds seemed of interest,

in particular, because a comprehensive survey of this type is not available in the literature. For convenience, the somewhat amorphous body of material in Part I has been arranged in three sections:

I. Bond Properties.

II. Differences between oxygen and sulphur compounds in reactions directly involving the heteroatom.

III. Effect of oxygen and sulphur on adjacent and more distant atoms.

The discussion has been restricted to the behaviour of the C - S, S - H, C - O and O - H bonds; no attempt has been made to compare S - S and O - O bonds or to discuss sulphoxides, sulphones and related compounds.

PART I

Discussion of the physical and chemical properties of analogous oxygen and sulphur compounds.

As already stated, sulphur atoms resemble oxygen atoms in their outermost electronic structure, but there are three major differences which affect the comparative chemistry of these elements very significantly:-

- (i) The sulphur atom has an underlying kernel of ten electrons compared to only two in oxygen. Sulphur atoms are therefore substantially lower in electronegativity than oxygen. The outer shell electrons are less tightly held and so sulphur compounds have smaller ionisation potentials and inductive effects, but greater polarisabilities.
- (ii) The greater physical size of the sulphur atom may exert a steric effect.
- (iii) Sulphur is able to expand its valence shell to ten electrons, utilizing d orbitals, whereas oxygen cannot; therefore sulphur and oxygen analogues may react with different mechanisms.

A more detailed discussion of individual chemical and physical properties of analogous oxygen and sulphur compounds, follows.

Section I : Sulphur and Oxygen Bond Properties

(i) Bond Angles.

In the lowest energy state of the oxygen atom, there are two unpaired electrons, each in a different p level (Fig. 1a). The valence bond theory in its simplest form

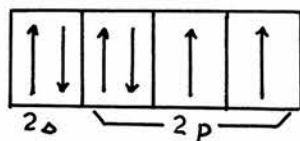


Fig. 1a

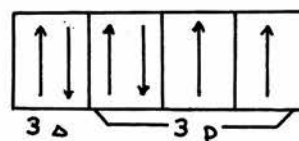


Fig. 1b

assumes that the bonds in, for example, H_2O are formed from these p orbitals, and it predicts, therefore, that the bond angle should be 90° . A similar argument holds for sulphur (Fig. 1b), other members of group VI, and also for nitrogen, phosphorus, etc., in Group V. The bond angles in PH_3 , H_2S and the higher members of both groups of molecules are in reasonably good agreement with this predicted value, but the bond angles in the H_2O and NH_3 molecules are much larger, and approach the tetrahedral angle (109.5°) (cf. Table I).

Table I. Bond Angles: Hydrides of Group V and VI⁽⁶⁾.

Molecule	Bond Angle °	Molecule	Bond Angle °	Electro- negativity
H ₃ N	107.3	H ₂ O	104.5	Decreasing
H ₃ P	93.3	H ₂ S	92.2	electro-
H ₃ As	91.8	H ₂ Se	91.0	negativity of
H ₃ Sb	91.3	H ₂ Te	89.5	central atom ↓

Repulsion between the hydrogen atoms and partial hybridisation of the orbitals of the central atom have been put forward as explanations of these apparently anomalous bond angles in H₂O and NH₃⁽⁷⁾. Mellish and Linnett⁽⁸⁾, however, argue as follows:- In a symmetrical environment, e.g. in N³⁻, O²⁻, the four electron pairs associated with the central atom (N,O) would have a regular tetrahedral arrangement, like those of carbon in CH₄. However, as discussed below, the effect of the lone pairs relative to the shared pairs in compounds such as NH₃ and H₂O, is such that the interbond angles are reduced below the tetrahedral value. Further, in compounds of the type AX₂ and also AX₃, the valence angle X - A - X appears to be correlated with the electronegativity of X and A. Thus in the absence of obvious steric effects, as the electron affinity of the outer atom increases (cf. Table 2) or

that of the central atom decreases (cf. Table 1), within the same group and with no change in the number of lone pairs, the angle between the bonds decreases.

Table 2. Substituent electronegativity : Bond Angle⁽⁹⁾.

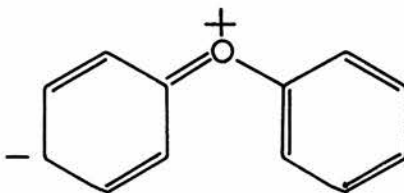
Compound R X R'	R O R' °	R S R' °	Electro- negativity
CH ₃ ·X;CH ₃	111	105 (99) [#]	Increasing
CH ₃ ·X·H	107-109	100·3	electro-
H·X·H	104·5	92·2	negativity of
F·X·F	103·8	-	substituent ↓

#Note : The value given in brackets is that obtained from a recent analysis by Pierce and Hayashi (1961)⁽¹²⁾.

When an electron pair is used to form a bond with a hydrogen nucleus, the electrons will tend to be concentrated more along the direction of the internuclear axis than in a lone pair, and repulsion between them and other electron pairs will decrease⁽⁶⁾. Thus in H₂O the angle (104·5°) is less than tetrahedral (109·5°) because the electrons in the two O-H bonds repel each other less than they are repelled by the more diffuse lone pairs. Further, because the

electronegativity of sulphur is less and its radius greater than that of oxygen, the bonding electrons in H_2S will be further from the central nucleus and closer to the hydrogen nuclei than they are in H_2O . Thus the bonding electron pairs are at a greater distance apart and occupy "slimmer" orbitals in H_2S , compared with H_2O . Therefore, in H_2S , repulsion between the bonding pairs is relatively smaller, and repulsion between the two lone pairs and the bonding pairs relatively greater, than the corresponding repulsions in H_2O . Hence the bond angle in H_2S is smaller than it is in H_2O . From Table 2 it is seen that the introduction of the more electronegative F atom in place of H in H_2O further reduces the interbond angle, while the electron-donating methyl group has the opposite effect.

When oxygen is attached to saturated carbon, the bond angle at oxygen is within a few degrees of the tetrahedral angle (except for small ring compounds) as is explained above. When oxygen is attached to an aromatic ring however, as in diphenyl ether, the lone-pair electrons on the oxygen can partially delocalise into the aromatic system; the O-C bonds acquire some double-bond character (II) and the bond angle increases to values considerably



greater than the tetrahedral (cf. Table 3). Similarly bond angles in aromatic sulphides are greater than in aliphatic sulphides.

Table 2. Bond Angles: Aromatic Ethers, Sulphides, etc. (6)

Compound	X	O	S	Se	Te
$(p\text{-CH}_3\cdot\text{C}_6\text{H}_4)_2\cdot\text{X}$		121°	109°	106°	101°
$(\text{C}_6\text{H}_5)_2\cdot\text{X}$		124°	106°(±4°)	-	-
$(p\text{-Br}\cdot\text{C}_6\text{H}_4)_2\cdot\text{X}$		124°	109°	-	-

(ii) Bond Lengths.

Table 4 contains, for comparison, some relevant bond lengths of analogous oxygen and sulphur compounds.

(iii) Van der Waal Radii.

Table 5 lists the Van der Waal radii of a few atoms. These Van der Waal radii are useful for assessing the presence of repulsions between non-bonded atoms in molecules, in connection with the possibility of steric hindrance.

Table 4. Bond Lengths : Selected O and S analogues⁽⁹⁾.

Compound	Bond Lengths. Å°			
	C - O	C - S	O - H	S - H
H ₂ O	-	-	0.96	-
H ₂ S	-	-	-	1.33
CH ₃ .OH	1.43	-	0.96	-
CH ₃ .SH	-	1.82	-	1.33
C ₂ H ₅ .O.C ₂ H ₅	1.43	-	-	-
C ₂ H ₅ .S.C ₂ H ₅	-	1.81	-	-
Paraldehyde	1.42(±.02)	-	-	-
Tristhio- acetaldehyde	-	1.81	-	-
C ₄ H ₄ O Furan	1.41(±.02)	-	-	-
C ₄ H ₄ S Thiophen	-	1.74(±.03)	-	-

Table 5. Van der Waal radii (Å°) : A selection^(10a).

H	O	S	Se
1.2	1.4	1.85	2.0
F	Cl	Br	I
1.35	1.80	1.95	2.15

(iv) Thermochemical Bond Strengths.

Both the bond dissociation energies and the thermochemical bond strengths of C - S bonds are less than those of C - O bonds. The same is true for S - H and O - H bonds. The specific values of the thermochemical bond strengths for bonds involving sulphur atoms depend on the values selected for other bonds, and on the value selected for the heat of atomisation of sulphur; the latter value is controversial. However, Table 6, gives the 1962 values of J.D. Cox⁽¹⁴⁾ together with some Pauling⁽¹⁵⁾ values (1952).

Table 6. Thermochemical Bond Strengths (K cal./mol.).

<u>Bond</u>	<u>Cox</u>	<u>Pauling</u>
O - H	108.7	110.6
S - H	81.9	81.1
C _{sp₃} - O	91.7	84.0
C _{sp₃} - S	65.7	62.0

(v) Electronegativity.

Pauling⁽¹⁰⁾ has built up, on an arbitrary basis, a scale of the individual values of the electronegativities (i.e. the power of an atom to attract electrons) of various atoms. Some of these values are included in Table 7, together

with the corresponding "first" ionisation energy of the atom. The "first" ionisation energy is a measure of the energy required to remove an electron from an atom in the ground state. As noted earlier both quantities are smaller for sulphur than for oxygen.

Table 7. Electronegativity^(11a); "1st." Ionisation Potential⁽¹¹⁾.

Element	Electro- negativity	1st. Ionisation Energy (k. cal./g. atom)
H	2.2	313
C	2.6	260
F	3.9	402
Cl	3.2	300
Br	2.8	273
I	2.5	241
O	3.5	314
S	2.6	239
Se	2.55	225
Te	2.3	208

(vi) Dipole Moment

The electric dipole moment of a molecule is a valuable characteristic of its structure, but the relation

between the dipole moment and the constitution is complicated, even for a diatomic molecule (i.e. one bond).

As Table 8 shows⁽¹³⁾, the dipole moments of the hydrides of the compounds of Groups V, VI and VII, decrease with increasing atomic number of the heavy elements in a vertical series (e.g. $\mu_{\text{H}_2\text{O}} > \mu_{\text{H}_2\text{S}}$) whereas the carbon compounds exhibit a maximum (underlined) at the second row element (e.g. $\mu(\text{CH}_3)_2\text{O} < \mu(\text{CH}_3)_2\text{S}$). The difference is difficult to explain with the usual electronegativity arguments.

Table 8. Dipole Moments : Groups V, VI and VII.

Group V Substituent H ₃ (CH ₃) ₃			Group VI Substituent H ₂ (CH ₃) ₂			Group VII Substituent H CH ₃		
N	107°	108°	O	104°	110°	F
	<u>1.47D</u>	0.65D		<u>1.85D</u>	1.30D		<u>1.91D</u>	1.81D
P	93.5°	100°	S	92.3°	99°	Cl
	0.55D	<u>1.45D</u>		0.92D	<u>1.40D</u>		1.08D	<u>1.37D</u>
As	92°	96°	Se	Br
	0.22D		0.80D	1.80D

Gibbs⁽¹³⁾ concludes that the lone-pair moments, which actually make the major contribution to the molecular moment, will be governed by (a) the size of the relevant

atomic orbitals, and (b) their degree of hybridisation (increasing s character of the lone-pair will decrease its moment). Thus the available bond-angle data (Table 8) indicate that the degree of hybridisation of the central atom decreases with increasing atomic number in a group of the Periodic Table, from nearly tetrahedral sp_3 toward $90^\circ p$ bonding, rapidly in the case of the hydrides, and slowly in the case of the carbon compounds (cf. page 6). Gibbs then suggests the following explanation of the dipole moment variations. If there was no loss in hybridisation, the lone-pair moment would increase with increasing atomic number, because of the increase in the orbital size. In the case of the organic compounds, this effect remains dominant until the third-row element is reached, because the decrease in hybridisation is slow. In the case of the hydrogen compounds, however, the loss in hybridisation at the second-row element is already very great and the moment is already decreasing.

Section II : Differences between oxygen and sulphur compounds
in reactions directly involving the heteroatom.

(i) Acidity and Basicity.

Hydrogen sulphide is more acidic than water, both in the first and second stages of ionisation (cf. Table 9).

Table 9. Dissociation Constants of Simple Hydrides⁽¹⁶⁾.

<u>Equilibrium</u>	<u>pKa</u>	<u>Acid</u>	<u>pKa</u>
$\text{H}_2\text{O} \rightleftharpoons \text{H}^+ + \text{OH}^-$	15.7	HF	3.2
$\text{H}_2\text{S} \rightleftharpoons \text{H}^+ + \text{HS}^-$	7.0	HCl	- 7
$\text{H}_2\text{Se} \rightleftharpoons \text{H}^+ + \text{HSe}^-$	4.0	HBr	- 9
$\text{H}_2\text{Te} \rightleftharpoons \text{H}^+ + \text{HTe}^-$	3.0	HI	- 11
$\text{HS}^- \rightleftharpoons \text{H}^+ + \text{S}^{2-}$	14.0		

From Table 9, it is seen that acid strength increases with rising atomic number (cf. H_2O , H_2S , H_2Se , H_2Te , and similarly cf. HF, HCl, HBr and HI). Again, mercaptans are considerably more acidic than alcohols; thus n-butylmercaptan has pKa 11.5 compared with ca. 16 for n-butanol⁽¹⁷⁾.

The above relationships are equivalent to the statement that RO^- and O^{--} are more basic than RS^- and $\text{S}^{=}$. A similar difference in basicity is shown by ethers

and thioethers. Unfortunately comparative data for the protonation of ethers and thioethers do not appear to be available, but a measure of the relative basicities can be obtained from a study of the equilibrium constants for the distribution of boron trifluoride between two ethers in benzene solution; the equilibrium constants were measured by infrared spectroscopy (cf. Sect. II, (ii)).



Some equilibrium constants for the above reaction are tabulated below (Table 10). These results show that

Table 10. Equilibrium Constants : $B_1 + B_2 : BF_3 \rightleftharpoons B_1 : BF_3 + B_2$ ⁽¹⁸⁾.

B_1	$B_2 : BF_3$	K
Tetrahydrofuran	$Et_2O : BF_3$	~ 500
Tetrahydropyran	$Et_2O : BF_3$	37 ± 2
Dimethyl ether	$Et_2O : BF_3$	4.5 ± 0.2
Diethyl ether	$Me_2O : BF_3$	0.24 ± 1
Diethyl sulphide	$Et_2O : BF_3$	0.0003
Tetrahydrothiophene	$Et_2O : BF_3$	0.016

diethyl ether is not a very strong base compared with cyclic ethers, but it is considerably more basic than

diethyl sulphide. Further, it has been shown by U.V. spectroscopy that the sulphur in thioamides is less basic towards protons than the oxygen in amides⁽¹⁹⁾.

The greater basicity of oxygen compounds compared with sulphur analogues is at first sight surprising since oxygen might be expected to be more reluctant to donate electrons to a proton than the less electronegative sulphur. However, similar relationships are encountered in other groups of the Periodic Table; thus ammonia is more basic than phosphine, and hydrogen chloride is a weaker acid than hydrogen bromide. These differences can in fact be explained in terms of the decrease in hybridisation which occurs as the atomic weight of the central atom increases; this effect has already been discussed in connection with bond angles and dipole moments. For example, the lone pair in phosphine has more s character than the lone pair in ammonia, and since s electrons are more tightly held, one can argue that the lone pair in phosphine will be less basic⁽²⁰⁾. A related and probably more satisfactory explanation, is that addition of a proton to phosphine (bond angle 93°) to give the tetrahedral (sp_3 hybridised) phosphonium ion must involve the expenditure of considerable "rehybridisation energy"⁽¹³⁾, this effect being much smaller in the case of ammonia (bond angle 107°).

It may be noted that neither of these arguments

will explain the greater basicity of O^- compared with S^- (or Cl^- compared with Br^-) and the following interpretation, based on an application of the arguments of Mellish and Linnett (cf. page 6) is tentatively advanced here. The ions O^- and S^- are tetrahedrally hybridised having four lone pairs, and the repulsion between these lone pairs will be greater for the smaller oxygen atom. Involvement of one of the lone pairs in a bond (e.g. with a proton) will decrease this repulsion (cf. page 8) and the oxygen might therefore be expected to welcome a proton more readily. This argument can be extended to explain the greater basicity of OH^- compared with SH^- , etc.

Table 11. Dissociation Constants of Various Alcohols and Mercaptans⁽¹⁷⁾.

<u>Substance</u>	<u>pKa</u>
Phenol	9.95
n-Butanol	16
Ethanol	18
Thiophenol	7.47
n-Butylmercaptan	11.51

Phenol is a stronger acid than the alcohols and similarly thiophenol is more acidic than aliphatic thiols

(cf. Table 11). These facts can be ascribed to the mesomeric distribution of the negative charge of the phenolate or thiophenolate ion into the ring, giving enhanced stability to the phenolate or thiophenolate ion.

The sulphur compounds are stronger acids than their oxygen analogues, but the difference :

$$(\text{pKa}) \text{ n-BuSH} - (\text{pKa}) \text{ PhSH} = 4.04$$

is smaller than the difference :

$$(\text{pKa}) \text{ n-BuOH} - (\text{pKa}) \text{ PhOH} = 6.05$$

in agreement with the concept of greater mesomeric electron donation to the aromatic ring by oxygen than by sulphur (cf. page 39).

(ii) Relative Co-ordinating Affinities of Ligand Atoms from the same group i.e. O, S, Se, Te.

Chatt et al⁽²¹⁾, consider that there is no uniform pattern of relative co-ordinating affinities of all ligand atoms for all acceptor molecules and ions, not even when only simple unidentate ligands of closely analogous structures are considered. Rather their relative affinities depend on the acceptor concerned (cf. Table 12). However, there is in general a very great difference between the co-ordinating affinities of the first and the second element from each of the three groups of ligand atoms in the Periodic Table, i.e. between N and P, O and S, F and Cl. In addition there are two classes of acceptor:

Table 12. Bivalent O, S, Se, Te as ligands.

<u>Acceptor</u>	<u>Ligand Affinities</u>
Trimethyl gallium	O > S < Se > Te
Platinum (II)	O ≪ S ≫ Se < Te
Silver	O ≪ S < Se < Te

(a) those which form their most stable complexes with the first atom of each group i.e. with N, O and F and (b) those which form their most stable complexes with the second or subsequent ligand atom. Most metals in their common valency states belong to class (a). It also contains the hydrogen ion, and therefore the affinities of ligands for class (a) acceptors tend to run roughly parallel to their basicities, except when steric or other factors intervene. As pointed out earlier (cf. page 17) the relative affinity of ligands for class (a) acceptors can be interpreted in terms of differences in hybridisation.

The behaviour of class (b) acceptors is generally ascribed to their tendency to form bonds involving the 3d orbitals of ligands in the second (or higher) periods. Silver and mercuric ions are typical class (b) acceptors and the fact that they give stable compounds with sulphur derivatives is well known.

Boron is of interest as a border element conforming

to neither class (a) nor class (b) acceptors (cf. Table 13).

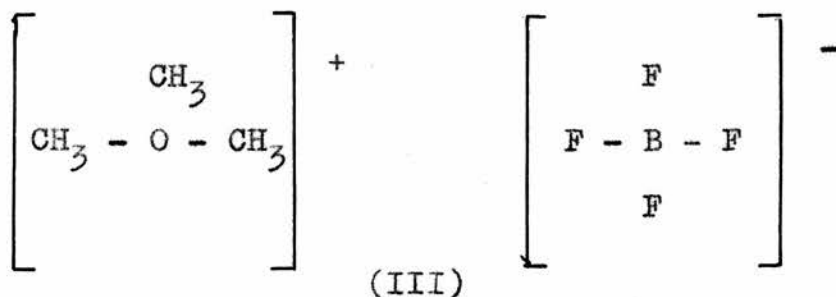
Table 13. Relative Affinities of O, S, Se for BR_3 ⁽²²⁾.

<u>Acceptor</u>	<u>Class</u>	<u>Relative Affinity</u>
BF_3	a	$\text{O} > \text{S} > \text{Se}$
BH_3	b (mild)	$\text{O} < \text{S} > \text{Se}$
BMe_3	b (mild)	$\text{O} < \text{S} > \text{Se}$

Chatt⁽²¹⁾ considers that the data relating to the group O, S, Se, Te, where sequences depend so much on subtle differences between the acceptor atoms, will be more valuable than any other in classifying the various acceptor molecules and ions according to their co-ordination chemistry.

(iii) Sulphonium and Oxonium Salts.

Oxygen and sulphur both form onium salts, the former being not very common and rather reactive. However, the isolation⁽²³⁾ of trimethyloxonium fluoborate (III), is direct evidence of the existence of oxonium salts.



Much more is known of the corresponding sulphonium salts, wherein sulphur is linked by single bonds to three atoms and hence bears a positive charge⁽¹⁷⁾. Unlike the corresponding oxygen compounds, such compounds are readily formed from thioethers and alkyl halides. It seems likely that their greater ease of formation and stability is due to stabilisation by hyperconjugation (1V), with the utilisation of the d-orbitals of the sulphur. In fact, CH_3^+ can be considered as a class (b) acceptor (see previous section).



(1V)

There is much evidence of the involvement of d-orbitals in the behaviour of sulphonium salts⁽²⁵⁾. For example, the ability of these groups to stabilise an adjacent carbanion is undoubtedly due to a combination of electrical and resonance factors (V).



(V)

(iv) Charge Transfer Bonds : Halogen to Sulphur and Oxygen.

The formation of complexes between halogens on the one hand and electron donors such as ethers and thioethers on the other, has been known for a long time, as witnessed by the colour difference of iodine in various solvents. For instance, solutions of iodine in aliphatic hydrocarbons, carbon disulphide, chloroform, are violet, the colour of iodine vapour, whereas, iodine in acetone, alcohols, ethers, benzene, give brownish solutions. The formation of such complexes is generally ascribed to "charge transfer interactions", the halogen acting as an acceptor. The theory has been reviewed in detail⁽²⁶⁾.

The complexes are often weak and are therefore dissociated to a considerable extent in solution. However, the equilibrium constants governing their formation can readily be determined spectroscopically, since the complexes show absorptions in the ultraviolet or visible regions which are not present in the spectra of the donor or acceptor alone. No data is available for oxygen-sulphur comparison, but Table 14 shows that the selenium compounds are more stable than the sulphur complex⁽²⁷⁾.

The formation of weak bonds between halogens and ethers or thioethers has also been revealed by X-ray diffraction studies⁽²⁸⁾. Thus the investigation of a number of the crystalline addition compounds formed between halogens and ethers or thioethers has shown that the O-Halogen

Table 14. Dissociation Constants of R_2SX_2 and R_2SeX_2 ⁽²⁷⁾.

<u>Compound</u>	<u>Dibromide</u>	<u>Di-iodide</u>
$(CH_3)_2S$	-	1.40×10^{-2}
$(CH_3)_2Se$	$<4 \times 10^{-7}$	2.12×10^{-3}
$(C_6H_5)_2Se$	$<4.8 \times 10^{-4}$	3.60×10^{-2}

and particularly the S-Halogen bond distances in these compounds are considerably smaller than the sum of the van der Waal radii, indicating that the adducts are not merely inclusion compounds (cf. Table 15). Further, a lengthening of the Hal-Hal bond is observed; this effect is quite marked for the sulphur compounds. The charge-transfer bond results in a linear or nearly linear arrangement: donor atom-halogen-halogen. In the case of the weak charge-transfer bonds formed by ethers and ketones, both halogen atoms of a particular halogen molecule can form simultaneously a "halogen molecule bridge" between two oxygen atoms.

It appears therefore, at least from crystal data, that the strength of charge-transfer interactions with the halogens falls in the order $Se > S > O$. Since the strength of charge-transfer bonds has been theoretically related to the ionisation potential of the donor, their order is not unexpected ⁽²⁶⁾.

Table 15. Bond lengths (\AA) in addition compounds with ethers and sulphides as donor molecules⁽²⁸⁾.

Compound	Charge-transfer bond	Bond Length	Sum of van der Waals radii	Hal-hal bond length	Bond length in free Hal	Angle donor-Hal-Hal
1,4-Dioxan, Br_2	O-Br	2.71	3.35	2.31	2.28	180°
1,4-Dioxan, 2ICl	O-I	2.57	3.55	2.33	2.32	-
1,4-Dithian, 2I_2	S-I	2.87	4.0	2.79	2.67	178°
1,4-Diselenan, 2I_2	Se-I	2.83	4.15	2.87	2.67	180°
Benzyl sulphide, I_2	S-I	2.78	4.0	2.82	2.67	179°

(v) Hydrogen Bonding.

The formation of a hydrogen bond⁽³¹⁾ in a solution or compound modifies a great many physical and a few chemical properties. Some of the more important physical property modifications are frequency shifts of IR and Raman bands, alterations in freezing and boiling points, solubility differences due to hydrogen bonding between solvent and solute, changed dielectric properties and p.m.r. shifts. For example, compounds which form intermolecular hydrogen bonds have high freezing and boiling points, because of the strong intermolecular forces. This is illustrated in Table 16 in which some properties of water, which forms strong

hydrogen bonds, are contrasted with those of hydrogen sulphide.

Table 16. Some physical properties of water and hydrogen sulphide.

Substance	Melting Point (°K)	Boiling Point (°K)	Heat of Vaporisation (k cal/mole)
H ₂ O	273	373	540 (at 373°K)
H ₂ S	190	231	132 (at 212°K)

The earlier work in the literature⁽²⁹⁾ suggested that thiols have little or no tendency to form hydrogen bonds, but Gordy and Stanford⁽³⁰⁾ have reported distinct IR evidence that mercaptans form hydrogen bonds with nitrogen bases such as pyridine. Pimentel and McClellan⁽³¹⁾ present many references supporting such hydrogen bonding, quoting evidence based on IR, UV, chromatography, etc. In Table 17 are tabulated the heat effects on mixing equimolar quantities of *n*-heptyl or phenyl mercaptan with four organic solvents. For comparison, corresponding heats of mixing with chloroform and phenyl acetylene are included⁽³²⁾.

The data show that whereas *n*-heptyl mercaptan gives no evidence of hydrogen bonding, the more acidic phenyl mercaptan

Table 17. Heat of mixing (cal/mole) at 3° for Equimolar mixtures⁽³²⁾.

	n-Heptyl mercaptan	Phenyl mercaptan	Phenyl- acetylene	Chloroform
N,N,dimethyl- acetamide	No heat	572	644	920
Ethyl ether	No heat	173	272	700
Acetone	No heat	150	200	-
Benzene	No heat	No heat	No heat	No heat

bonds to the donor atoms, oxygen or nitrogen, but the S-H←O or N bonds are considerably weaker than the C-H←O or N bonds formed by chloroform. From the evidence presented, it is clear that the -S-H group does show hydrogen bond association with donors, but that these bonds would appear to be much weaker than the corresponding bonds formed with -O-H; definite thermodynamic evidence on this point would however be desirable.

Evidence that the sulphur atom can act as a base in hydrogen bonding is now fairly well established, IR showing the hydrogen bonding of thioamides and thioethers in solution⁽³³⁾ crystal structure that of 2-thiopyridone⁽³⁴⁾, kinetic studies that of disulphides⁽³⁵⁾, etc. The Thermodynamic results of the interaction of phenol with certain

compounds and the spectral shifts due to hydrogen bonds are listed in Table 18^(36, 37); these results provide several points of interest.

Table 18 shows that sulphur and selenium give spectral shifts similar to oxygen, and the Badger-Bauer rule⁽³⁸⁾ (relating the spectral shift in cm^{-1} , from the 'free' to the 'bonded' peaks, directly to the strength i.e. enthalpy of the hydrogen bond) might lead to the deduction that the hydrogen bonds formed are of the same strength. In fact the ΔH values show that the S and Se bonds to hydrogen are much weaker. Similarly, the ΔH values for the halides show a decrease in hydrogen bond strength in the order $\text{F} > \text{Cl} > \text{Br} > \text{I}$ (electronegativity order), with increasing spectral shift. Similar conclusions are reached for hydrogen bonding to tetrahydropyran and tetrahydrothiapyran.

(vi) Sulphur and Oxygen Compounds as Nucleophiles.

In nucleophilic bimolecular substitution reactions of the type:-



where N is a nucleophilic reagent and SX is a substrate containing a replaceable group X and an electrophilic atom S, there are many factors which affect the rate of reaction e.g. polarisability and basicity of the nucleophilic atom, solvation effects, steric effects. For this reason, generalisations concerning nucleophilic activity are hard to make,

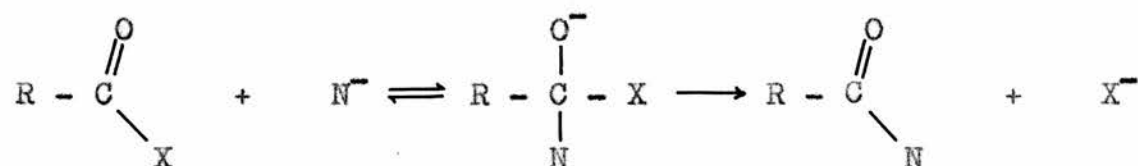
TABLE 18.
Thermodynamic Properties and Spectral Shifts of Hydrogen
Bonds of Phenol to Alkyl Halides and Alkyl Chalcogenides. (36,37)

Donor	Solvent	ν_{OH} (cm^{-1})	$K_{Assoc.}$ (l/mol.)	$-\Delta H^{\circ}$ (k cal/mol.)	$-\Delta F^{\circ}$ (25°C) (k cal/mol.)	$-\Delta S^{\circ}$ (25°C) (k cal/mol.)
Cyclohexyl fluoride	Chloroform	53	-	3.13	1.31	6.1
" chloride	"	66	-	2.21	0.87	4.5
" bromide	"	82	-	2.05	0.85	4.0
" iodide	"	86	-	1.72	0.82	3.0
n-Butyl ether	"	278	-	5.98	2.45	11.8
n-Butyl sulphide	"	254	-	4.26	1.59	9.0
n-Butyl selenide	"	240	-	3.72	1.46	7.6
Tetrahydrothiapyran	"	244	1.187	2.99	0.10 (30°)	9.5 (30°)
Tetrahydropyran	Tetrachloro- ethylene.	290	7.07	4.32	1.18 (30°)	10.3 (30°)

especially as the activity of the nucleophile depends on the particular substrate undergoing attack e.g. tetrahedral carbon, aromatic carbon, carbonyl carbon, etc.

However, Edwards and Pearson⁽³⁹⁾ and Hudson⁽⁴⁰⁾ have examined this type of reaction and agree that the results obtained can be correlated with differences in basicity and polarisability[#] of the nucleophile; Hudson, in addition, points out that a decrease in the solvation energy of the nucleophile will also lead to an increase in nucleophilic attack, a factor neglected by Edwards and Pearson.

In the case of displacements at Carbonyl Centres the basicity (Edwards and Pearson), or, more precisely (Hudson), the strength of the bond formed between N and S, would appear to be the most important factor. For example, in the reaction:-



Note : Polarisation of the prospective bonding electrons in the direction from N towards S, would permit better electrostatic interaction between these two reactants, without bringing in Pauli exclusion effects due to the rest of the N molecule. Similarly, polarisation of the non-bonding electrons on N away from S may reduce Pauli repulsions.

the intermediate is tetrahedral⁽⁴¹⁾ and may go on to product or revert to starting material; hence the rate depends on the relative strengths of the N-C or X-C bonds e.g. oxygen nucleophiles would be expected to be more effective than their sulphur analogues. Thus SCN^- which is a stronger nucleophile than OH^- towards saturated carbon (cf. below) is a very much weaker nucleophile than OH^- towards acyl carbon^(40a). Polarisability, which would give sulphur nucleophiles an advantage over oxygen nucleophiles, does not seem to play a significant part in such reactions.

From their interpretation of relevant reaction data for nucleophilic attack on Saturated Carbon, Edwards and Pearson suggest that both polarisability and basicity factors are significant, the former being rather more important. They give the following order of reactivity:- $\text{O}_4\text{H}_9\text{S}^- > \text{C}_6\text{H}_5\text{S}^- > \text{S}_2\text{O}_3^{2-} > \text{SC}(\text{NH}_2)_2 > \text{I}^- > \text{CN}^- > \text{SCN}^- > \text{OH}^- > \text{N}_3^- > \text{Br}^- > \text{C}_6\text{H}_5\text{O}^- > \text{Cl}^- > \text{C}_5\text{H}_5\text{N} > \text{CH}_3\text{CO}_2^-$. The difference in reactivity of analogous oxygen and sulphur compounds is illustrated by the rate constants of the reaction of thiophenolate anion and phenolate anion with n-butyl bromide which are 1.28×10^{-2} and 1.31×10^{-5} respectively. Such differences are interpreted in terms of the greater polarisability of sulphur, although, as mentioned earlier, it is possible that the fact that the PhS^- anion has a smaller solvation energy, may also be partly responsible.

Edwards and Pearson suggest that in the case of nucleophilic attack on Aromatic Carbon both polarisability and

basicity of the nucleophile play a part, the latter being rather more important than in the case of saturated carbon; they give the following order of nucleophilic strength:-
 $\text{C}_6\text{H}_5\text{S}^- \approx \text{CH}_3\text{O}^- > \text{C}_5\text{H}_{10}\text{NH} > \text{C}_6\text{H}_5\text{O}^- > \text{N}_2\text{H}_4 > \text{OH}^- > \text{C}_6\text{H}_5\text{NH}_2 > \text{Cl}^- > \text{CH}_3\text{OH}$. In particular in contrast to the situation in nucleophilic attack on saturated carbon, where PhS^- is stronger than EtO^- or MeO^- by a factor of ca. 10^3 (42); MeO^- and PhS^- react at approx. equal rates. However, PhS^- is more reactive than PhO^- by ca. 10^2 (cf. Table 19).

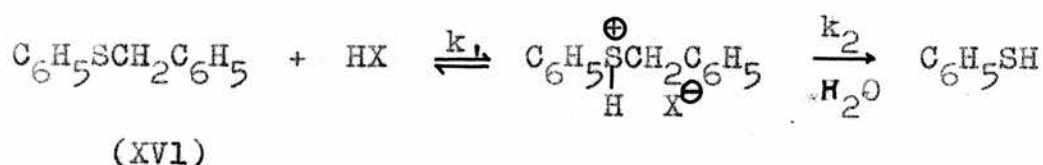
Table 19. Rate Constants at 25° for 4-fluoronitrobenzene with nucleophile X⁽⁴²⁾.

X	OMe^-	SPh^-	OPh^-	$\text{C}_6\text{H}_5\text{NH}_2$	Cl^-
k	1.8×10^{-4}	1.68×10^{-4}	$\sim 10^{-6}$	1.56×10^{-8}	1.71×10^{-14}

(vii) Cleavage of the Carbon-Sulphur bond.

(a) Thioether cleavage. Three- and four- membered sulphur-containing rings are easily cleaved, as are three- and four- membered cyclic ethers, but this ease is not exhibited by tetramethylene sulphide or tetrahydrothiapyran; both are stable to long treatment with dilute acid or base⁽⁴⁵⁾.

The sulphide (XVI) is not readily cleaved by aqueous halogen acids, although the analogous oxygen ethers are rapidly cleaved.⁽⁴⁶⁾ This is probably due to an unfavourable



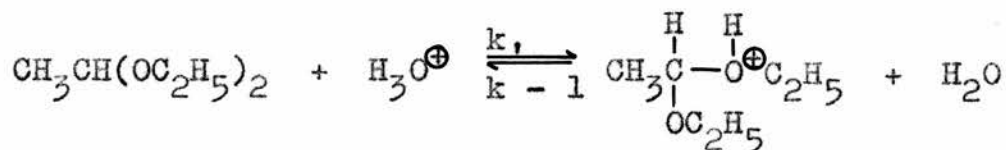
equilibrium in the first step although it might also be ascribed to a low value of k_2 . Similarly, the ArSCH_3 group resists cleavage by acidic reagents, compared to ArOCH_3 .

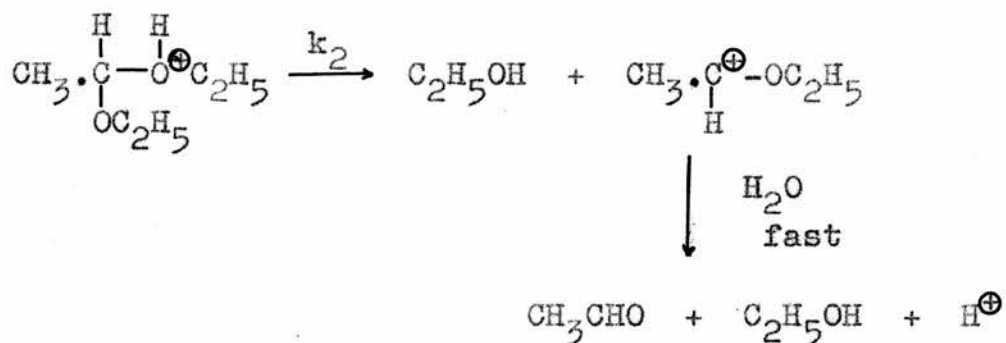
The generalisation that a C-S bond is rapidly cleaved when an unsaturated group is attached to the carbon is widely applicable⁽⁴⁵⁾. Thus, if B^- is a base, R is H or alkyl and Y is an unsaturated group (carbonyl, carboxyl etc.) the process may be represented as follows:



The fact that RS^- is a better leaving group than RO^- is presumably related to the lower bond strength of the C-S bond.

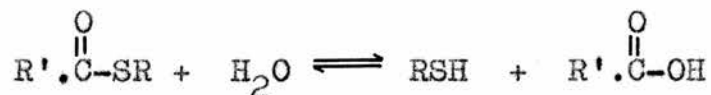
(b) Thioacetal cleavage. Hydrochloric acid alone is not very effective in cleaving the C-S bond of thioacetals, in contrast to its action with acetals; but mercuric chloride is often effective alone (curiously, the rate of the cleavage reaction with the latter is greatly increased by the addition of hydrochloric acid⁽⁴⁵⁾). The mechanism of the hydrolysis (hydronium-ion-catalysed) of acetals is considered to be as follows⁽⁵⁰⁾:





Again it would appear that, as was also the case in the cleavage of sulphides, the stability of thioacetals in acid solution is due to an unfavourable protonation equilibrium. By contrast, the formation of the mercury complex is more favoured.

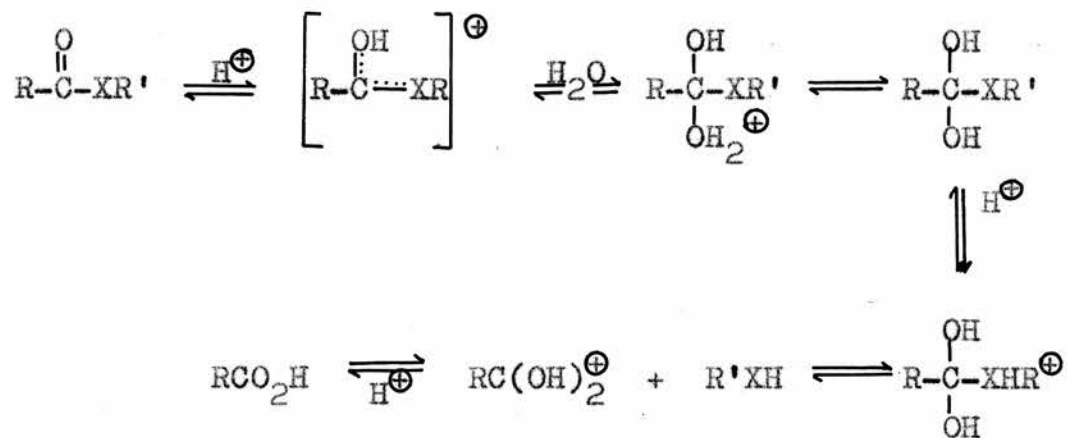
(c) Thiol ester cleavage. Measurements of the equilibrium between mercaptans and carboxylic acids show that the equilibrium is much less favourable to the thiol esters than the



corresponding one is to the oxygen esters⁽⁴⁷⁾; the position of the equilibrium is probably related to the lower resonance stabilisation of thiol esters (cf. p. 43)

It has been reported⁽⁴⁵⁾ that the rates of hydrolysis, using hydrochloric acid show that the thiol esters hydrolyse much more slowly than the oxygen esters, probably due to a slow protonation step in the thiol ester hydrolysis. By contrast, it has been reported that the alkaline hydrolysis

Acid Hydrolysis.



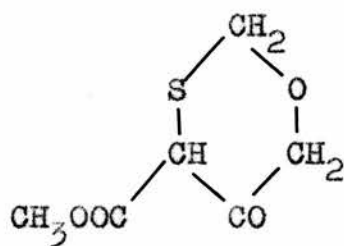
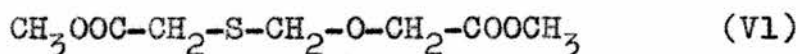
X = S or O

of alkyl thiolacetates and those of the corresponding oxygen esters are of the same magnitude.

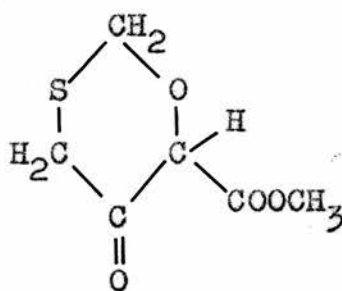
Section III : Effect of oxygen and sulphur on adjacent and further removed atoms.

(i) Acidity of adjacent C-H.

There is abundant evidence⁽²⁵⁾ that sulphur has a strong activating influence on the hydrogen atoms of an α -carbon; indeed, this acidifying effect of sulphur is often stronger than that of oxygen. Thus, when compound (VI) undergoes the Dieckman condensation, the product is (VII) and not (VII1)⁽²⁴⁾; this result is contrary to that expected from a consideration of simple inductive effects ($O > S$).

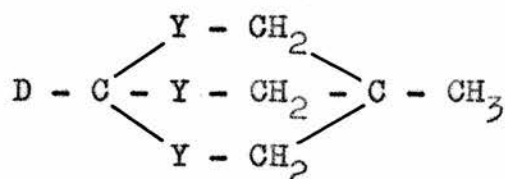


(VII)

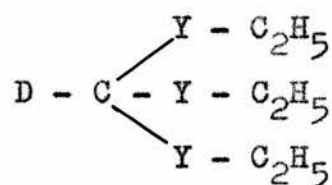


(VII1)

Again in a study of base-catalysed deuterium-hydrogen exchange reactions⁽⁴³⁾, it was found that compounds (IX) and (X) where Y = S, exchanged deuterium for hydrogen, whereas with their oxygen analogues (Y = O) no exchange took place.

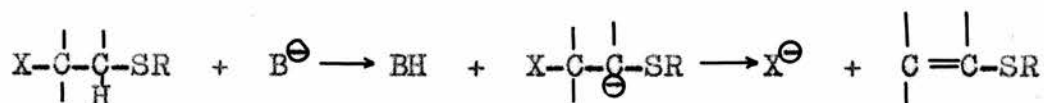


(1X)

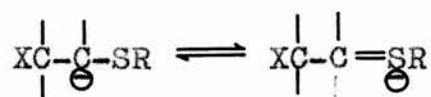


(X)

Similar activation of the α -hydrogen by an SR group explains the elimination of β -placed nucleophilic groups (X = SC_2H_5 , OC_2H_5 , OH etc.) by base, thus :



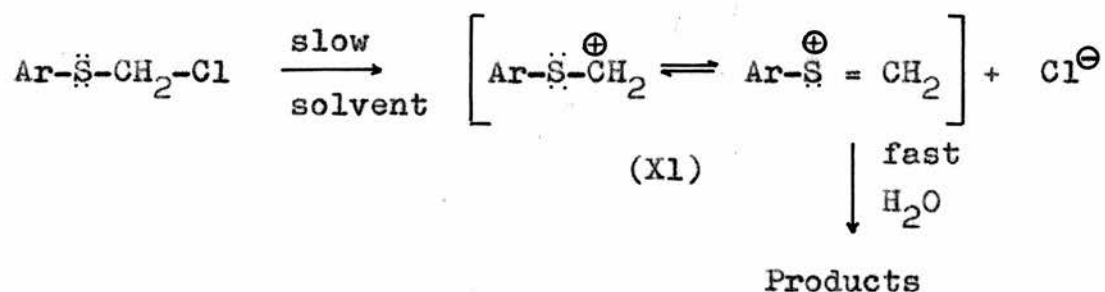
In general, then, the SR group promotes the uptake of the electron pair which binds the α -hydrogen, presumably because sulphur can stabilise an adjacent carbanion by resonance with a decet structure⁽⁴⁴⁾.



(ii) Effect of adjacent O/S on $\text{S}_\text{N}1$ reactions : Solvolysis of α -Chlorosulphides.

α -Chloroalkyl sulphides, such as dichloromethyl sulphide are extremely reactive compounds and hydrolyse spontaneously when mixed with water. Recently the mechanism

of the hydrolysis of chloromethyl alkyl or aryl sulphides was studied⁽⁵⁴⁾; it was found that the hydrolysis follows first-order reaction kinetics, and by analogy with the corresponding oxygen compounds (see below) it is thought to proceed by the S_N1 mechanism. The reaction may thus be schematically expressed in the following manner:-



Because of participation by the sulphur atom in the resonance stabilisation of the resulting carbonium ion (X1) chloromethyl sulphides are at least several thousand times more reactive to hydrolysis than is n-butyl chloride⁽⁴³⁾.

The oxygen analogues, chloromethyl alkyl ethers, are still more reactive in solvolytic reactions under S_N1 reaction conditions. For example, chloromethyl ethyl ether hydrolyses in aqueous dioxane about 1,600 times faster than chloromethyl ethyl sulphide^(48a), supporting the concept that oxygen, through contributions involving 2p-2p π -bonding between oxygen and carbon, is considerably more effective than sulphur as an electron donor. This may be explained as follows^(17a):-

When a 2p and a 3p orbital interact to form a π -bond

(as in the formation of the intermediate $\text{Ar}-\overset{+}{\text{S}}=\text{CH}_2$), the overlap will soon involve some anti-bonding interactions (Fig. II, doubly shaded portion), which are absent when a $2p-2p\pi$ -bond is formed (as in the formation of the intermediate $\text{Ar}-\overset{+}{\text{O}}=\text{CH}_2$). Thus π -bonds from $2p$ and $3p$ orbitals will be less favourable than those from two $2p$ orbitals.

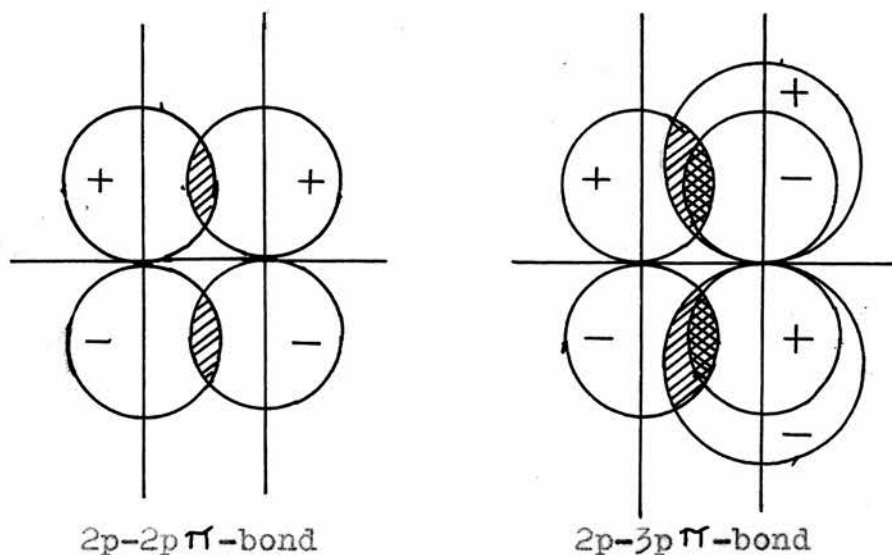
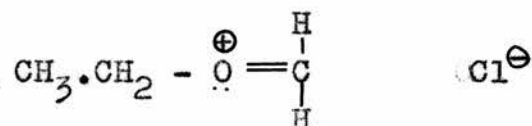


Fig. II

In other words, the +M electron-donating effect of oxygen is greater than that of sulphur. This had been noted earlier by Ingold⁽⁵¹⁾ who has provided a somewhat similar though probably less satisfactory explanation, namely that because of the overlap principle, double bonds are the more easily formed when the atoms concerned, in particular, the p orbitals of their valency shells, are of about the same size.

(iii) Effect of adjacent O/S on S_N2 reactions.

In a typical second-order nucleophilic substitution (S_N2) reaction such as with potassium iodide in acetone, chloromethyl ethyl sulphide reacts⁽⁵⁵⁾ about 5,000 times as fast as n-butyl chloride⁽⁵⁸⁾, while chloromethyl ethyl ether was found to react far faster than the sulphur analogue⁽⁵⁵⁾. The greater reactivity of the α -ethoxy compound ($\text{CH}_3\text{CH}_2\text{OCH}_2\text{Cl}$) compared with n-butyl chloride can be explained^(50a) by the mesomeric effect of contributions like:-



which facilitate bond-breaking in the transition state. This argument is closely similar to that used to explain the accelerating effect of the alkoxide group on S_N1 reactions (cf. p.38). Probably the α -ethoxy group increases the reactivity more than the α - SC_2H_5 group, because of the greater +M effect of oxygen. In addition, however, the greater size of the $-\text{SC}_2\text{H}_5$ group may cause a certain amount of steric hindrance, always an important factor in S_N2 reactions.

(iv) Effect of more remote oxygen and sulphur.

(a) Effect on acid strengths. A comparison of the acid strengths of substituted acetic acids reveals that the electron-attracting (acid-strengthening) properties of the $\text{CH}_3\text{O}-$ and $\text{C}_6\text{H}_5\text{O}-$ groups are greater than those of the corres-

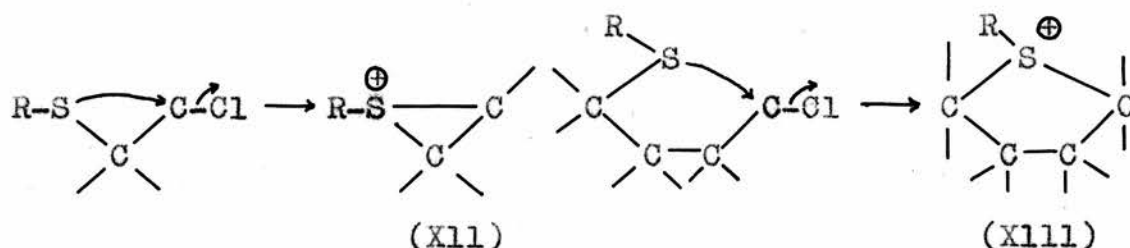
ponding sulphur compounds (cf. Table 20).

Table 20. Acid strength of substituted acetic acids⁽⁴⁹⁾.

<u>Substituent X</u>	<u>pKa</u>	<u>X.CH₂.COOH</u>
H-	4.76	
Cl-	2.86	
C ₆ H ₅ S -	3.52	
C ₆ H ₅ O-	3.12	
CH ₃ S-	3.72	
CH ₃ O-	3.53	

(b) Neighbouring group reactions. We have seen above, how the reactions of an organic molecule can be accelerated or retarded by groups which lie near the reaction site; the action of these groups was attributed to inductive, mesomeric or steric effects. However, in neighbouring group reactions, a group in the same molecule facilitates a displacement reaction by becoming fully or partially bonded to the reaction centre.

From the data in Table 21 (overleaf) it is seen that the hydrolyses of β - and δ -chlorosulphides are much more rapid than those of the analogous chloroethers. The reaction of the sulphur compounds are thought to proceed through cyclic sulphonium ions of the type (X11) and (X111).



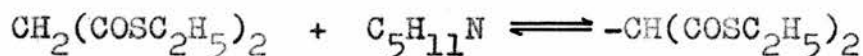
By contrast, α -chloroethers are hydrolysed much faster than the corresponding α -chlorothioethers (cf. page 37). γ -Chloroethers and γ -chlorothioethers are hydrolysed at about the same rate⁽⁴⁸⁾.

Table 21. Hydrolysis of alkyl ethers and sulphides in water/dioxan at 100° (48).

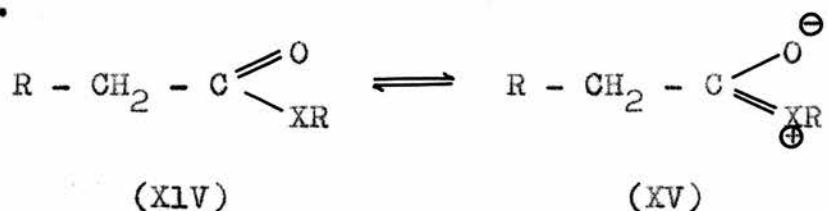
<u>Compound</u>	<u>$k \times 10^{-5}$</u>	
	<u>X=O</u>	<u>X=S</u>
$\text{Cl}(\text{CH}_2)_2 \cdot \text{X} \cdot \text{C}_2\text{H}_5$	1.1	17,000
$\text{Cl}(\text{CH}_2)_2 \cdot \text{X} \cdot \text{C}_6\text{H}_5$	0.6	550
$\text{Cl}(\text{CH}_2)_2 \cdot \text{X} \cdot (\text{CH}_2)_2\text{Cl}$	1.5	6,400
$\text{Cl}(\text{CH}_2)_3 \cdot \text{X} \cdot \text{C}_2\text{H}_5$	4.8	6.3
$\text{Cl}(\text{CH}_2)_3 \cdot \text{X} \cdot \text{C}_6\text{H}_5$	2.3	2.9
$\text{Cl}(\text{CH}_2)_4 \cdot \text{X} \cdot \text{C}_6\text{H}_5$	5.2	110
<u>n-Butyl chloride</u>	<u>6.2×10^{-5}</u>	

(c) α -Hydrogen reactivity of thiol esters. Cronyn and co-workers⁽⁵²⁾ have shown that in the piperidine-catalysed Knoevenagel reaction of benzaldehyde with ethyl malonate

and ethyl dithiomalonate, the thiol ester reacts four-times faster than the ester. It would appear from this and other evidence⁽⁵³⁾ that the α -hydrogen of thiol esters is more active than the corresponding ester.



This difference is readily explained as follows:- Esters are stabilised by resonance between the forms XIV and XV.

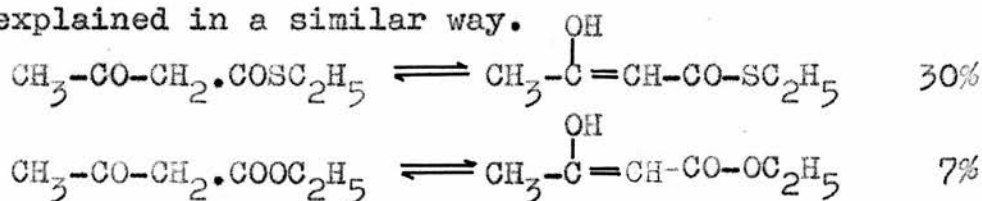


In the formation of the anion:



the resonance energy of the ester group is largely lost because of cross-conjugation; hence esters are less acidic than ketones. However, in thiolesters, resonance stabilisation due to participation of the form XV is considerably less, because of the smaller +M effect of sulphur and the acidity of thiolesters therefore lies between that of esters and ketones.

The fact that ethyl acetothiolacetate contains more enol form at equilibrium than ethyl acetoacetate⁽⁵³⁾ can be explained in a similar way.



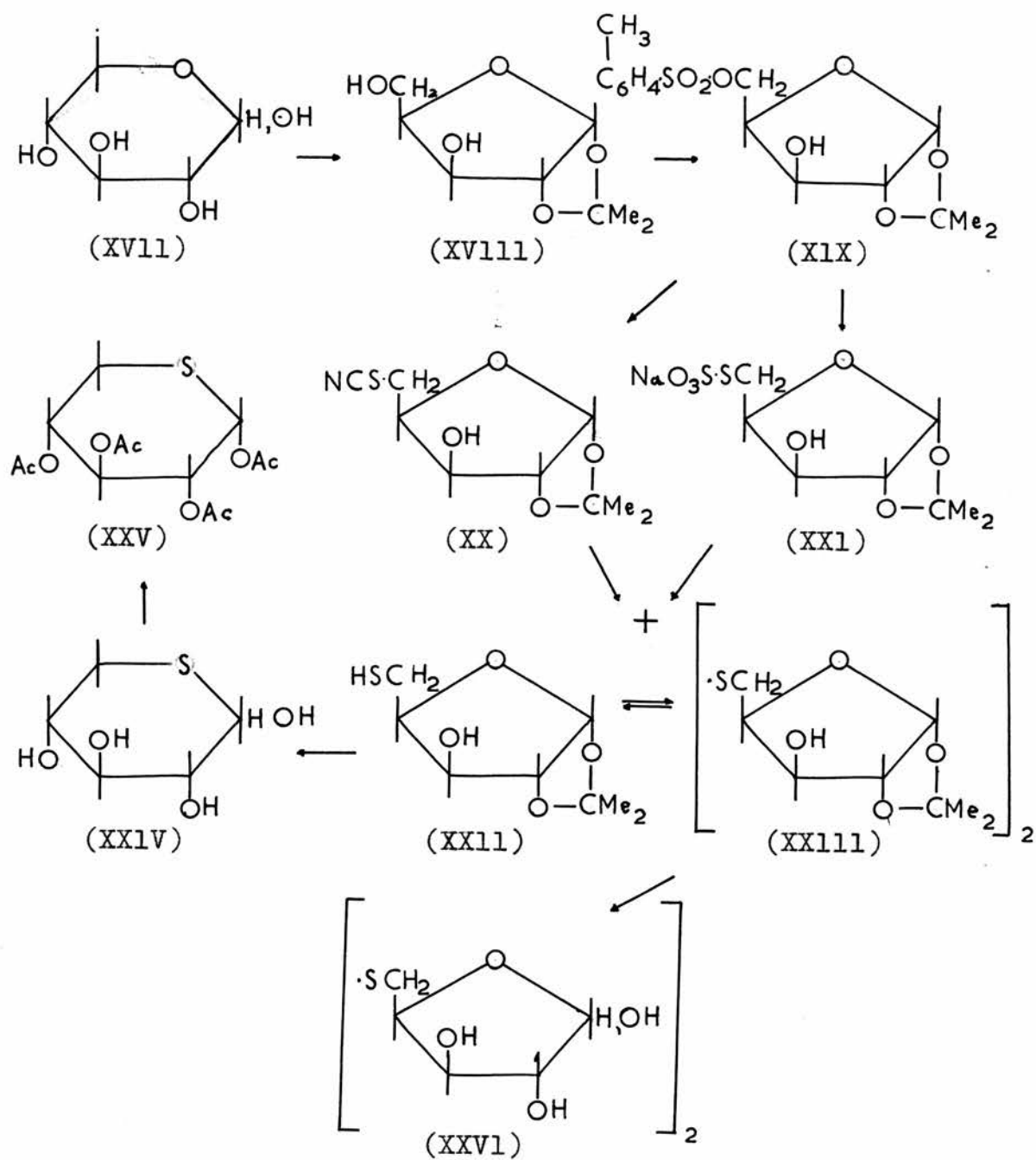
The above detailed discussion of the chemical and physical properties of analogous oxygen and sulphur compounds, clearly provides much support for the initial argument (p. 4) that the differences arise principally from three sources:

- (i) Different underlying electronic structure.
- (ii) Greater physical size of the sulphur atom.
- (iii) The expansion of the sulphur valence shell, utilising d orbitals.

PART II5-Deoxy-5-Thio-D-Xylopyranose and its DerivativesSection I : Preparation and Properties of 5-deoxy-5-thio-D-xylopyranose

(i) Preparation of 5-deoxy-5-thio-D-xylopyranose.

The route chosen for the preparation of the above sugar is shown in the reaction scheme on p. 46. 1,2-O-isopropylidene-D-xylofuranose (XVlll) was obtained⁽⁵⁶⁾ by the partial hydrolysis of 1,2; 3,5-di-O-isopropylidene-D-xylofuranose prepared⁽⁵⁷⁾ by shaking D-xylopyranose (XVll) in acetone with anhydrous copper sulphate and a little sulphuric acid. The 5-p-toluenesulphonate (XlX) was prepared⁽⁵⁷⁾ in the usual way by treating (XVlll) with p-toluenesulphonyl chloride in pyridine. By heating the 5-tosylate (XlX) with sodium thiocyanate in acetone in a sealed tube at 120°, 5-deoxy-1,2-O-isopropylidene-D-xylofuranose 5-thiocyanate (XX) was obtained⁽⁶⁰⁾. This reaction was capricious and also inconvenient to carry out. However, a search of the literature showed that a mixture of sodium and potassium thiocyanates (NaSCN, 30 mol.%; KSCN, 70 mol.%) formed a eutectic melt at 130°. By heating the 5-tosylate in this melt, we were able to obtain the 5-thiocyanate (XX), without undue decomposition of the sugar taking place. It seems likely



that similar use of low-melting salt media might be of value in other fields.

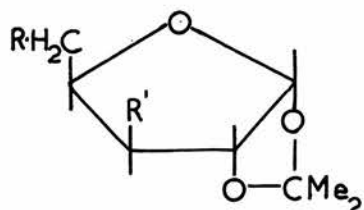
By reducing the 5-thiocyanate with sodium sulphide⁽⁶⁰⁾ or potassium borohydride, 5-deoxy-1,2-O-isopropylidene-D-xylofuranose 5-thiol (XX11) was obtained, together with some of the corresponding disulphide (XX111). The 5-thiol was obtained much more conveniently by heating the 5-tosylate with sodium thiosulphate in aqueous dimethylformamide (50% v/v) and reducing the resulting Bunte salt, 5-deoxy-1,2-O-isopropylidene-D-xylofuranose 5-(monosodium thiosulphate) (XX1) with potassium borohydride after removal of the dimethylformamide. Again the 5-disulphide (XX111) was obtained as a side-product but this could be reduced by lithium aluminium hydride in anhydrous ether to the 5-thiol. The 5-thiol was purified by subliming it twice at ca. 100° under reduced pressure (ca. 0.2 mm.). The 5-thiol (XX11), when oxidised with iodine, yielded the 5-disulphide (XX111).

The "sugar with sulphur in the ring", 5-deoxy-5-thio-D-xylopyranose (XX1V) was prepared either by hydrolysis of the 5-thiol with dilute sulphuric acid (0.1N) at 80° or, in a very pure form, by hydrolysis of the thiol under even milder conditions (Amberlite IR-120 at room temperature). The sugar was crystalline and, by the latter method, chromatographically pure. With acetic anhydride in pyridine, 5-deoxy-5-thio-D-xylopyranose gave a dextrorotatory tetraacetate (XXV); with acetic anhydride in the presence of

sodium acetate it gave the same tetra-acetate, with a smaller quantity of an isomeric laevorotatory acetate.

The disulphide (XXIII) was hydrolysed with Amberlite IR 120 and also with dilute sulphuric acid (0.1N) at 80°, and bis(5-deoxy-D-xylofuranose) 5,5' disulphide (XXVI) isolated crystalline. The latter compound was acetylated with acetic anhydride and pyridine but the product (possibly three isomeric hexa-acetates, α, α' ; β, β' and $\alpha\beta'$) could not be crystallised. Similar acetylation of the 5-thiol (XXII) also yielded a syrup.

Simultaneously with the publication⁽⁴⁾ of a short note of the above results, Adley and Owen⁽⁵⁹⁾ published a note intimating that they too had obtained 5-deoxy-5-thio-D-xylopyranose and the dextrorotatory acetate (XXV). Their precursor was also the 5-thiol (XXII) which they prepared by a somewhat different route. They treated 1,2-O-isopropylidene-5-O-tosyl-D-xylofuranose (XIX) with potassium thiolacetate in boiling dimethylformamide and obtained a mixture



(XXVII:R = SAc, R' = OH)

(XXVIII:R = SH, R' = OAc)

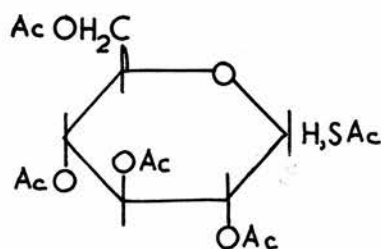
of the S-acetyl compound (XXVII) and (mainly) its rearrangement product, the O-acetate (XXVIII). Deacetylation of the mixture gave the 5-thiol (XXII) which they hydrolysed with

aqueous acid to give 5-deoxy-5-thio-D-xylopyranose.

(ii) Proof of the S-ring, its conformation and the configuration of the anomeric acetates.

(a) UV and IR spectra of the anomeric acetates.

When both of the anomeric tetra-acetates (dextro and laevo) of the sulphur sugar were analysed by ultra-violet spectroscopy, neither was found to absorb in the region λ_{max} . ca. $230 \text{ m}\mu$ which is the characteristic absorption region for simple thiolacetates⁽⁶¹⁾ e.g. glucothiose penta-acetate (XXIX).



$\lambda_{\text{max.}}$ $224 \text{ m}\mu$
 ϵ , 7500

(XXIX)

Further, neither spectra showed any indication of the presence of a disulphide grouping in the region of $250 \text{ m}\mu$ (ϵ 430)⁽⁶²⁾. However, in the spectra of both acetates there is a band at about $210 \text{ m}\mu$ ($\epsilon \sim 300$) which is similar to the absorption band at ca. $210 \text{ m}\mu$ ($\epsilon \sim 1000$) to be found in the spectra of dimethyl sulphide, and in cyclic sulphides such as thiacyclopentane and thiacyclohexane⁽⁶⁷⁾. Similar examination of the tetra-acetates by IR spectroscopy showed that neither acetate exhibited the characteristic absorption for the C=O stretching

vibrations in a thioester (1675 cm^{-1}); both acetates exhibited C=O stretching vibration absorption in the 1750 cm^{-1} region, characteristic of normal saturated esters⁽⁶³⁾.

The above data show that the two tetra-acetates, (XXV) and its anomer, cannot have furanose or disulphide structures and this, together with the evidence described under (b) and (iii), strongly supports the view that the parent sugar exists in the "thiapyranose form".

(b) Reaction of 5-deoxy-5-thio-D-xylopyranose with iodine and acidified 2,6-dichlorophenol indophenol.

When the 5-thiol (XXII; 0.01g) was dissolved in KH phthalate (0.005M) and titrated with iodine (0.0102 N) the reaction was instantaneous; the actual iodine titre (5.11 ml.) was slightly greater than the calculated amount required (4.77 ml.). However, when 5-deoxy-5-thio-D-xylopyranose (0.01g) was dissolved in KH phthalate (0.005M) and one-tenth of the theoretical quantity of iodine required, added, decolourisation of the iodine (starch indicator) took approx. 8 secs. ; as each successive 'one-tenth' portion was added, decolourisation became progressively longer. When the 5-deoxy-5-thio-D-xylopyranose (0.01g) was dissolved in KH phthalate (0.5M) the reaction was instantaneous and quantitative (Actual titre : 5.94 ml. ; calculated titre : 5.93 ml.).

In a similar series of experiments with 2,6-dichlorophenol indophenol, a reagent for the detection of thiol groups⁽⁸⁰⁾, the 5-thiol (XXII) in KH phthalate buffer A

(see (iii) below) caused the immediate decolourisation of this reagent. However, when 5-deoxy-5-thio-D-xylopyranose was dissolved in KH phthalate buffer A (pH 4.4), decolourisation of the 2,6-dichlorophenol indophenol reagent took several hours.

From the results with the 2,6-dichlorophenol indophenol reagent it was concluded that there was little or no thiol present in the 5-deoxy-5-thio-D-xylopyranose solution and that the slow decolourisation of the reagent paralleled the mutarotation reaction in this buffer (see (iii) below) i.e. production of the intermediate free thiol was slow. The instantaneous decolourisation of iodine in 0.5M phthalate can be ascribed to general-base catalysis of the ring-opening. However, even in 0.005M phthalate buffer the rate of decolourisation of iodine is greater than would be expected from the results with indophenol and it seems possible that iodine catalyses the opening of the sulphur ring through the initial formation of a charge-transfer complex (see p. 23).

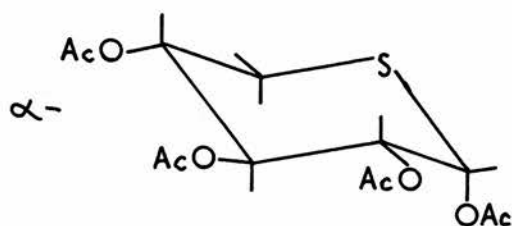
(c) Nuclear magnetic resonance spectra of the anomeric tetra-acetates.

The two anomeric tetra-acetates dextro- and laevo-rotatory, were originally designated α - and β - respectively, on the basis of their rotations⁽⁶⁴⁾. However, this procedure may not be reliable for the sulphur-ring sugars (no evidence to the contrary has been offered up to the present time, but see ref. 65). However, the fact that the laevo-rotatory

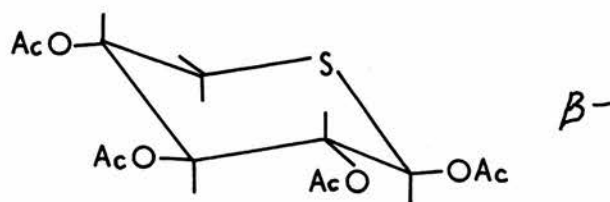


acetate melted at a higher temperature than the dextro-rotatory acetate supported this assignment (similar behaviour is shown by other acetylated D-glucose and D-xylose derivatives - the β -anomers have flatter molecules, since the group at C₍₁₎ is equatorial, and this presumably facilitates packing in the crystal lattice). Further support came from the relative mobilities of the compounds on paper chromatography with dimethyl sulphoxide as the stationary and di-isopropyl ether as the mobile phase⁽⁶⁶⁾.

However, to confirm the assignment, the nuclear magnetic resonance spectra of the two anomers were obtained and interpreted by Dr. Andrew Porte, of Glasgow University. He concluded that if the conformation is C₁, then it followed from the proton magnetic resonance of the $-S-\overset{|}{\underset{|}{\text{CH}}}-\text{OAc}$ proton, that the dextro-rotatory anomer is (XXX) and that the laevo rotatory anomer is (XXXI).



(XXX)



(XXXI)

Lemieux and co-workers⁽⁶⁸⁾ have carried out n.m.r. analysis of several aldopentopyranose and aldohexopyranose acetates, including the α - and β -D-xylose tetra-acetates.

They concluded that there are normally four groups of signals present in the n.m.r. spectrum of an aldopentopyranose acetate, and that these groups can be assigned to the different kinds of hydrogens in the molecule, through inspection of the intensities, positions and fine structure of the bands. The anomeric hydrogen is responsible for the signal which occurs at lowest field in the region of 3.88 - 4.63 τ . This hydrogen is unique in that it is the only hydrogen which is attached to a carbon which is bonded to two oxygen atoms.

In Table 22 are recorded the chemical shifts and coupling constants for the anomeric protons of the α - and β -tetra-acetates of the sulphur sugar and its oxygen analogue.

Table 22. Chemical Shifts and Coupling Constants for Anomeric Protons of D-xylopyranose and 5-deoxy-5-thio-D-xylopyranose tetra-acetates.

Compound	Chemical Shifts (τ values)	Coupling Constant J_{H_1, H_2} cycles/sec.	Config. at C_1
5-deoxy-5-thio- <u>D</u> -xylopyranose	4.03	2.4	α
tetra-acetate	4.03	8.5	β
(68) <u>D</u> -xylopyranose	3.97	3.0	α
tetra-acetate	4.62	6.0	β

It has been shown by several workers⁽⁷⁹⁾ that the magnitudes of the coupling constants between vicinal protons are related to the dihedral angle between the two C-H bonds. The large value for the coupling constant $J_{H_1H_2}$ for the β -anomers is in agreement with the expected order of magnitude for an axial-axial orientation, while the smaller values for the α -anomers indicate an axial-equatorial arrangement.

The α - and the β - tetra-acetates of the sulphur sugar have chemical shifts of the same value; normally, as in the case of the D-xylopyranose tetra-acetates, the signal from an equatorial proton (α -) occurs at a lower field⁽⁶⁹⁾. Now the relative shift between axial and equatorial hydrogens is a function of the diamagnetic anisotropy of nearby bonds or rings and the inductive effects of neighbouring atoms or groups. Jackman⁽⁷⁰⁾ has shown that the anisotropy of the carbon-carbon single bond is directed so that the resonance of an axial hydrogen is forced to a higher field than that of an equatorial hydrogen. However, Campaigne Chamberlain and Edwards⁽⁷¹⁾ have shown that the axial hydrogens in α -trithioacetaldehyde resonate at lower fields than the equatorial hydrogen, and suggest that the anisotropy of the carbon-sulphur single bond is opposite in sense to that of the carbon-carbon single bond. This observation may help to explain the results reported above for the α - and β -tetra-acetates of the sulphur sugar.

(d) Conformation of the Sulphur sugar ring.

On the day on which we prepared methyl 5-deoxy-5-thio-D-xylopyranoside (see p.72) we learned that a third laboratory had entered the "sulphur in the ring" field; Whistler, Feather and Ingles⁽⁷²⁾ reported the preparation of methyl 5-deoxy-5-thio-D-xylopyranoside. Recently Rao, Foster and Whistler⁽⁶⁹⁾ reported the nuclear magnetic resonance spectra of methyl 5-deoxy-5-thio- α and β -D-xylopyranosides and the free sugar, and concluded that at least for the β -compound, the spectrum is in accord with the C₁ ring conformation. In addition, they reported that the signal of the anomeric proton of the α -methyl glycoside appeared at a lower field than the corresponding β -anomer. (cf. the results in the previous section). Their results are shown in Table 23.

(iii) Mutarotation of 5-deoxy-5-thio- α -D-xylopyranose.

It has been known for many years that, when a freshly prepared solution of a sugar is examined polarimetrically, there is a change of optical rotation with time. This phenomenon is known as mutarotation. Sugars can be divided into two groups; firstly, those whose mutarotation exhibits first-order reaction kinetics, and secondly, those whose mutarotation is more complicated. The mutarotations of the first group are considered to involve a simple equilibrium between α - and β -anomers e.g. α -Glucose $\xrightleftharpoons{\text{equil.}}$ β -glucose

+ 112°	+ 52.7°	+ 18.7°
--------	---------	---------

Table 23. Chemical Shifts and Coupling Constants for the Anomeric Protons of the Methyl Glycosides of D-xylopyranose and 5-deoxy-5-thio-D-xylopyranose⁽⁶⁹⁾.

Compound	Chemical Shifts (τ values)		Coupling Constant $J_{H_1 H_2}$ cycles/sec.	Dihedral Angle deg.
	H_{1e}	H_{1a}		
<u>D</u> -xylose	4.82	...	2.2	60
	...	5.45	7.2	148
Methyl β - <u>D</u> -xylopyr- anoside	...	5.62	7.2	148
5-deoxy-5-thio- <u>D</u> - xylopyranoside	5.0	...	2.5	57
	...	5.25	8.2	154
Methyl 5-deoxy-5-thio- α - <u>D</u> -xylopyranoside	5.35	...	2.8	55
Methyl 5-deoxy-5-thio- β - <u>D</u> -xylopyranoside	...	5.52	8.4	156

The mutarotations of the second group involve two simultaneous or consecutive reactions, one of which is slow and the other rapid; e.g. the mutarotation of L-ribose involves a decrease from an initial value of $+23.4^\circ$ to a minimum of $+18.2^\circ$ and then a rise to a constant value of $+23.2^\circ$. It has been suggested that the slower reaction involves an α , β -conversion

between pyranose forms, and the fast mutarotation may represent pyranose-furanose interconversions⁽⁷³⁾.

We have shown that the mutarotation reactions of 5-deoxy-5-thio- α -D-xylopyranose and its oxygen analogue conform to the first-order equation and presumably mainly involve an α - and β -pyranose equilibrium. This, together with the somewhat unusual pH dependence of the mutarotation rate of the thiosugar (see below), provides further evidence that this sugar exists mainly in the pyranose form i.e. sulphur in the ring. The rate constants for the two sugars at 25.7° in potassium hydrogen phthalate buffer A (pH 4.4) and in potassium hydrogen phthalate - sodium hydroxide buffer B (pH 6.45) are shown in Table 24.

Table 24. Rate constants for mutarotation at 25.7°.

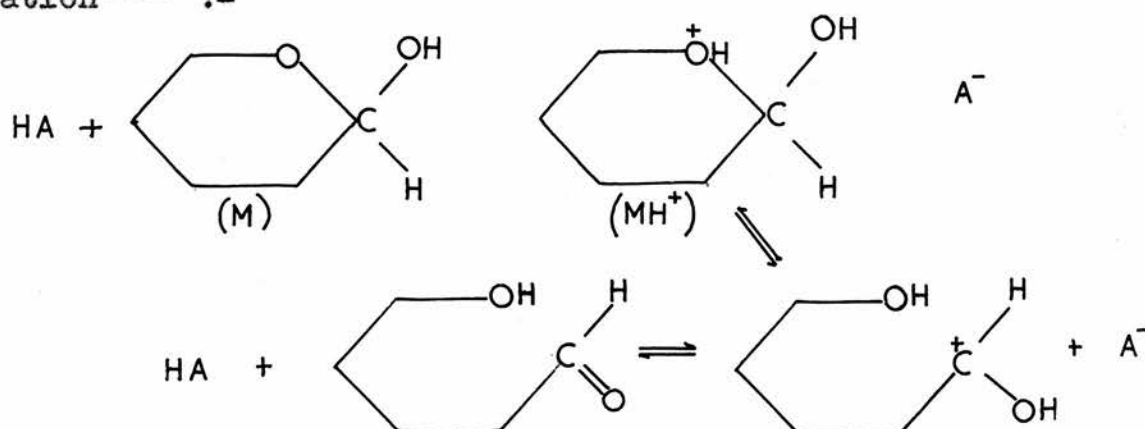
Compound	Buffer A [#]		Buffer B [#]		Equil. [¥]
	$t_{\frac{1}{2}}$ (min)	$k \times 10^3$ (sec ⁻¹)	$t_{\frac{1}{2}}$ (min)	$k \times 10^3$ (sec ⁻¹)	% α
5-deoxy-5-thio- α -D-xylopyranose	5.25	0.0207	8.25	1.32	ca. 80%
α -D-xylopyranose	8.10	1.42	7.55	1.53	ca. 20%

[#] See experimental for details.

[¥] Note. Neither the β -anomer of 5-deoxy-5-thio-D-xylopyranose

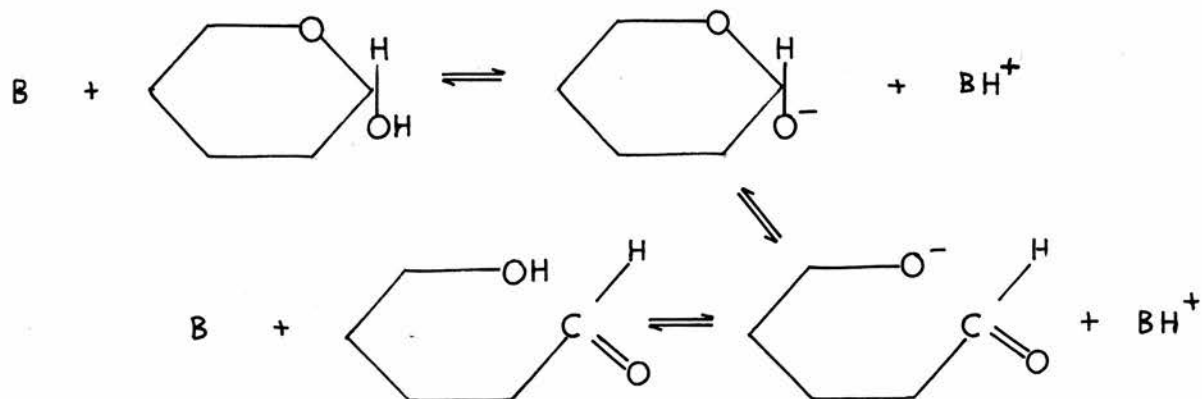
nor the β -anomer of D-xylopyranose have been isolated, but a value for their specific rotations can be calculated from the specific rotations of their respective α - and β -methylglycosides and the α -isomer of the free sugar, using Hudson's Isorotation rule⁽⁷⁸⁾.

The mutarotation reaction exhibits general acid and base catalysis⁽⁷⁴⁾, the rate depending on the concentrations of all the acids and bases present. The mechanism generally accepted for mutarotation involves conversion to the open-chain form[#]; for example for the acid-catalysed mutarotation⁽⁷⁵⁾ :-



Note. A mechanism involving protonation of the O₁ followed by fission of the C₁-O₁ bond is excluded by the observation that the exchange of O¹⁸ between D-glucose and water is much slower than the mutarotation reaction. See D. Rittenberg and C. Groff, J. Amer. Chem. Soc., 1958, 80, 3370.

Again, a mechanism suggested for the base-catalysed reaction⁽⁷⁵⁾ :-



As has already been stated, the mutarotation reaction is catalysed by both acids and bases. Even at pH values < 7, there will still be base catalysis, and indeed, Isbell and Pigman⁽⁸³⁾ have shown for several sugars that the minimum mutarotation constants are in the region of pH 4.6. Thus for glucose at 20°, the rate constant is given by :-

$$k = 0.0060 + 0.18[\text{H}^+] + 16,000[\text{OH}^-]$$

From the results in Table 24 we see that at pH 6.45 the mutarotation of 5-deoxy-5-thio-D-xylopyranose is only slightly slower than that of D-xylopyranose. However, at pH 4.4 the mutarotation of D-xylopyranose shows little change, whereas 5-deoxy-5-thio-D-xylopyranose mutarotates about sixty times slower. This indicates that acid catalysis of the mutarotation of the thiosugar must be relatively slight even at pH 4.4 (if it were entirely absent the

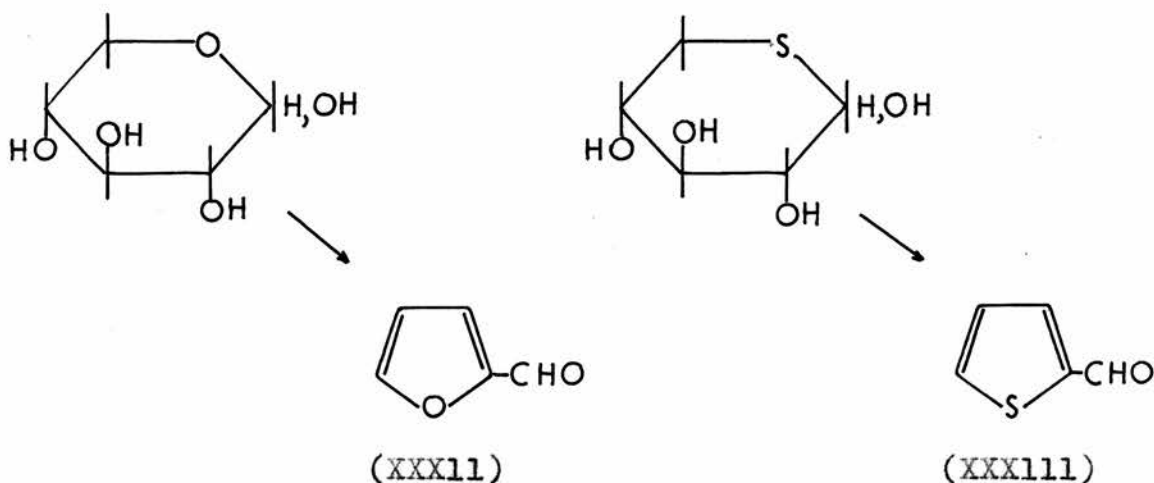
mutarotation rate at pH 4.4 would be ca. one hundredth of that at pH 6.45). The ineffectiveness of acid catalysis is evidently due to the fact that sulphur is less readily protonated than oxygen (cf. p. 34). It is clear that a detailed examination of the pH - rate profile for the mutarotation of the thiosugar would be of considerable interest.

The relative proportions of the α - and β -anomers at equilibrium for D-xylopyranose (α = ca. 20%) and its thiosugar analogue (α = ca. 80%) are also of interest. The relative stabilities of the anomers of a sugar or sugar derivative (e.g. a glycoside) appear to depend on two opposing factors : (i) the usual preference of groups for the less hindered equatorial orientation, and (ii) the presence of electrostatic interactions^(77, 84) between the anomeric group and the oxygen of the ring - these favour the axial (α -) orientation. Thus the fact that the equilibrium (in methanol) between the anomeric glucosides or xylosides favours the α -anomer, is explicable in terms of the second factor. In aqueous solutions of the sugars, however, the dipoles are heavily solvated; consequently, electrostatic interactions are reduced and the equatorial β -anomer is favoured. Since sulphur is a poorer acceptor for hydrogen bonds than oxygen, it is reasonable to account for the predominance of the α -anomer in the mutarotation equilibrium of the sulphur sugar in terms of decreased solvation. Further, the dipole interaction between the ring sulphur and the

anomeric oxygen may, in any case, be slightly greater (the dipole moment of dimethyl sulphide > dipole moment of dimethyl ether (cf. p. 13)) than that for D-xylopyranose. Unfortunately, the observation that the relative ease of hydrolysis of the anomeric methyl xylosides is approximately the same for the oxygen and sulphur compounds, seems difficult to reconcile with this view (cf. p. 79).

(iv) Reaction with concentrated acids.

The action of hot concentrated acids on sugars produces profound changes involving the formation of anhydro rings or double bonds. For example, when D-xylopyranose is boiled with 12% (w/v) hydrochloric acid, 2-furfuraldehyde (XXX11) is produced in nearly quantitative yield. When



5-deoxy-5-thio-D-xylopyranose was treated with 12% (w/v) hydrochloric acid, 2-thiophenylaldehyde (XXX111), identified as its p-nitro-phenylhydrazone, was produced. A simple experiment involving distillation of the sugars with 12% (w/v)

hydrochloric acid, showed that 2-thiophenalddehyde was produced faster from 5-deoxy-5-thio-D-xylofuranose than furfural was from the corresponding oxygen sugar. It was also shown that 2-thiophenalddehyde was liberated fairly rapidly when the thio-sugar was treated with 2N hydrochloric acid at 60°; these conditions had no effect on D-xylopyranose.

The reason for the greater lability of the thiosugar to acid is not clear, since the mechanism of these reactions is inadequately understood. However, it seems probable that the first step is the dehydration (by β -elimination) of the aldehydo-sugar⁽⁸¹⁾ and the proportion of this may possibly be greater for the sulphur analogue. The formation of furan compounds from hexose sugars has been reviewed by Newth⁽⁸²⁾.

Section 11 : Preparation, Reactions and Methanolysis of 2,3,4-tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranosyl 1-bromide

- (i) Preparation of 2,3,4-tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranosyl bromide.

The fully acylated glycosyl halides, particularly the acetylated compounds, are very well known. They are among the most important intermediates for synthesis in carbohydrate chemistry; moreover, the chemistry of these poly-O-acyl halides is of considerable intrinsic interest. Glycosyl halides have been used in the preparation of orthoesters, thio- and seleno-sugars, anhydro sugars, oligosaccharides, glycals etc. . The glycosyl halides and their derivatives have been reviewed by Haynes and Newth⁽⁸⁵⁾.

It seemed of interest, therefore, to prepare the acetobromo derivative of the sulphur sugar, not only for the qualitative study of some of its reactions, but also for a comparison of its reaction products and rates with those of the corresponding oxygen sugar. 2,3,4-Tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranosyl 1-bromide was prepared by the usual method by the reaction of 5-deoxy-5-thio- α -D-xylopyranose tetra-acetate with hydrogen bromide in acetic acid. The acetobromo compound is thought to have the α -configuration, because of its positive rotation ($[\alpha]_D = + 240^\circ$, c 1.5 in chloroform) although the actual value of this rotation is

rather smaller than might be expected.

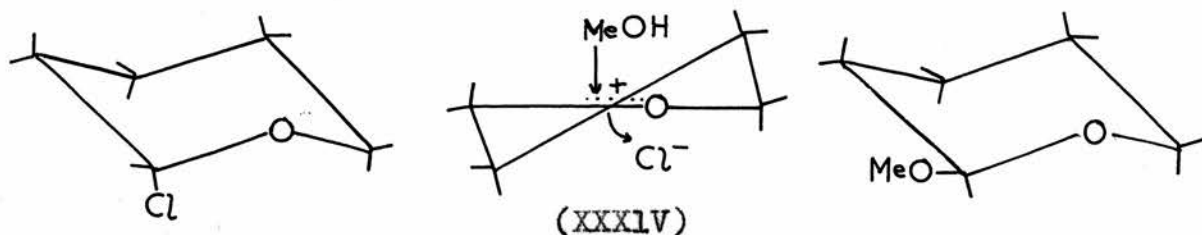
(ii) The Koenigs-Knorr reaction and the reaction of the acetobromide with silver acetate.

The reaction of an acylated glycosyl halide with an alcohol in the presence of certain electrophilic catalysts, e.g. silver carbonate, is known as the Koenigs-Knorr reaction⁽⁸⁶⁾. This reaction has received considerable attention^(87, 88) regarding the influence of the acetoxy groups on the course of replacement reactions at C_1 ; the kinetic order of the reaction has also been a subject of controversy⁽⁸⁷⁻⁹¹⁾. The kinetic aspect will be dealt with later, but the essential difference between the reactions of 1,2-trans- and 1,2-cis-O-acetyl glycosyl halides will be considered now.

When the halogen is cis to an O-acetyl group at C_2 , reaction with a nucleophilic reagent gives glycosides with a high degree of inversion at C_1 . On the other hand, a trans disposition of the halogen with respect to the neighbouring acetyl group leads to the formation of a considerable amount of the 1,2-orthoacetate, together with the anomeric α - and β -glycosides⁽⁸⁸⁾.

Mattock and Phillips have shown⁽⁹²⁾ that the rates of solvolysis of tetra-O-acetyl- α -D-glucosyl 1-halides in water-acetone and methanol-acetone in the presence of mercuric salts as catalyst, are proportional to the first power of both sugar halide and mercuric salt concentrations. Mercuric

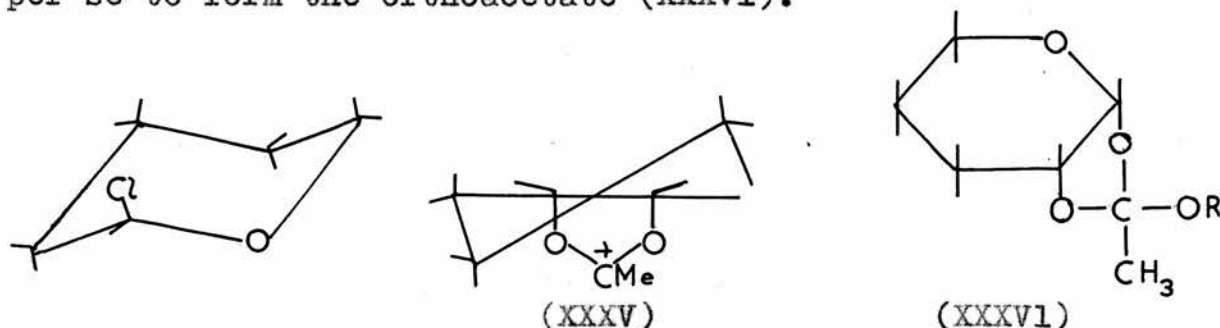
salts were used in place of silver salts to avoid complications due to a heterogeneous medium and also to the catalytic effect of precipitated silver halides. Citing evidence by Hughes, Ingold and others⁽⁹³⁾ they postulate a mechanism for these reactions which involves the rate-determining formation of a carbonium-ion intermediate, as in the uncatalysed S_N1 solvolysis of these compounds. For the 1,2-cis-acetoxy-halides they propose the following reaction mechanism⁽⁹⁴⁾, involving the intermediate carbonium ion (XXXIV) in the half-chair conformation:-



Entry of the substituting group is predominantly on the side leading to inversion. This could be due to obstruction of the entering group by the departing group on the side leading to retention of configuration, or alternatively, to the attack by a solvent molecule on an ion pair, as postulated by Lemieux and Huber⁽⁹¹⁾ and also favoured by Rhind-Tutt and Vernon⁽⁹⁵⁾. Shielding by substituent groups may also be a contributing factor.

For the 1,2-trans-acetylglycosyl halides, Mattock and Phillips⁽⁹⁴⁾ postulate the participation by the neighbouring 2-acetyl group to form a cyclic-ion intermediate (XXXV) and

point out the importance of the 3-group in determining the reactivity. Lemieux and Brice⁽⁹⁶⁾ also arrived at a similar conclusion regarding the reactivity of 1,2-trans-sugar acetates. The cyclic-ion intermediate (XXXV) can undergo further unimolecular solvolysis to give the trans glycoside or react per se to form the orthoacetate (XXXVI).



When 2,3,4-tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranosyl bromide was treated with methanol in the presence of silver carbonate, the product obtained was methyl 2,3,4-tri-O-acetyl-5-deoxy-5-thio- β -D-xylopyranoside, and its α -isomer in the ratio of about 3 : 2. The fact that the β -isomer predominates and the fact that no orthoacetate was detected, provide further evidence indicating that the aceto-bromo-sugar has the α -configuration. Again when the aceto-bromide was treated with silver acetate in glacial acetic acid, the β -tetra-acetate and the α -tetra-acetate were produced in the proportions 3 : 2 (approx.).

The production of a considerable amount of α -isomers in the above reactions is in marked contrast to the behaviour of the corresponding tri-acetyl- α -D-xylopyranosyl 1-bromide and similar 1,2-cis-acetohalogeno sugars, which give mainly

the 1,2-trans-isomers.. The methanolysis (uncatalysed) of the thiosugar bromide also gives a considerable proportion of the α -anomer (see Section 111). This behaviour is difficult to explain. One possible explanation is that, because of the greater C-S bond length, shielding by the departing bromide ion is less, and the reaction therefore tends to produce the thermodynamically more stable α -anomer, particularly since, as suggested by the mutarotation equilibrium (Section 1), this anomer appears to be especially favoured in the case of the sulphur compounds. From the results it may be concluded that the above reactions of 2,3,4-tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranosyl 1-bromide are typical of normal S_N1 reactions i.e. racemisation occurs.

(iii) Methanolysis of 2,3,4-tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranosyl bromide.

The methanolysis experiments with the sulphur sugar acetobromide and its oxygen analogue were carried out in a thermostatted cell and observed polarimetrically using an ETL - NPL photoelectric polarimeter coupled to a Honeywell-Brown potentiometric recorder. The rate constants for the reaction are shown in Table 25. Full details of the procedure may be found in the Experimental.

The methanolysis of acetobromoxylose gave an excellent first-order plot; complications from autocatalysis by the liberated hydrogen bromide (cf. Newth and Phillips⁽⁹⁷⁾) were not encountered, presumably because the concentration of the

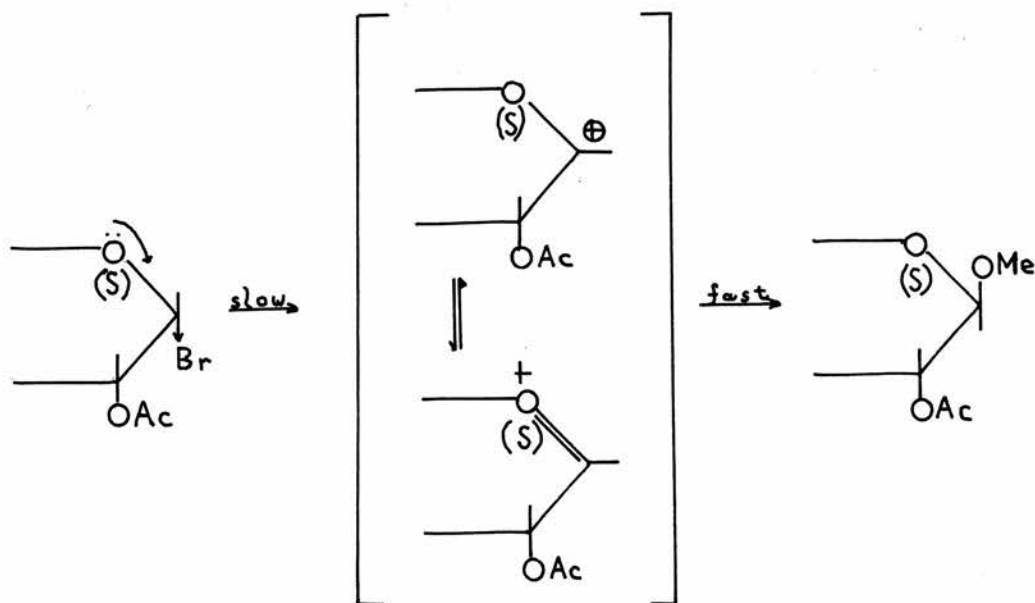
Table 25. Rate constants (duplicates) for the methanolysis of the acetobromo sugars at 25.5° .

Compound	$t_{\frac{1}{2}}$ (min)	$k \times 10^5$ (sec ⁻¹)
Tri- <u>O</u> -acetyl- α - <u>D</u> -xylopyranosyl bromide	5.30	217.9 ^a
	5.25	220.0 ^a
Tri- <u>O</u> -acetyl-5-deoxy-5-thio- α - <u>D</u> -xylopyranosyl bromide	214.80	5.374 ^a 5.374 ^b
	207.60	5.468 ^a , 5.632 ^b
<p>a. Calculated from the slope of the plot $r_t - r_\infty$ against t where r_t = rotation at time t r_∞ = rotation at infinity (> 10 half-lives)</p> <p>b. Calculated by the Swinbourne method⁽⁹⁸⁾ (see Experimental)</p>		

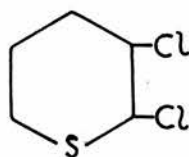
acetobromo sugar was low (ca. 0.3%). However, the methanolysis of the sulphur analogue showed a noticeable departure from first-order behaviour after ca. three half-lives. Examination of the products after ten half-lives showed the presence of methyl 5-deoxy-5-thio-D-xylopyranosides indicating that deacetylation is probably responsible (cf. ref. 97). However, examination by thin-layer chromatography indicated that the amount of deacetylation was small in the early stages of the reaction; the rate constants in Table 25 were calculated

from the first two half-lives and are not likely to be greatly in error. This was confirmed by calculation of the rate constants by the method of E.S.Swinbourne⁽⁹⁸⁾ using the data from the first two half-lives of the reaction. Despite the considerable amount of deacetylation which had occurred after ten half-lives, both the experimental infinity value and the infinity value obtained by the Swinbourne method were almost identical; of course, this is purely a coincidence.

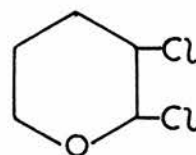
It is generally agreed that the solvolysis of the acetylglycosyl halides in the absence of an acid acceptor follows a unimolecular mechanism⁽⁸⁵⁾. It has also been pointed out⁽⁹⁹⁾ that the high reactivity of these compounds is typical of the α -halogeno ethers (cf. p. 37). The S_N1 mechanism seems to be preferred because the inductive polarisation of the C-halogen bond is reinforced by electromeric release from the oxygen atom, thus facilitating the ionisation of the halogen. The mechanism of the reaction can be represented thus :



Oxygen is known to enter into electron donor type resonance to a larger extent than sulphur (cf. p. 38) ; hence one would expect it to have a greater effect than sulphur in promoting the ionisation of the α -halogen. The experimental results which we have obtained are in agreement with this, as we have found that the oxygen-ring sugar reacts about forty times faster than its sulphur analogue. Comparison of the rates of methanolysis of other α -haloethers and thioethers agrees with the above interpretation of the results. Thus Newth and Phillips⁽¹⁰⁰⁾ have shown that 2,3-dichlorothiacyclohexane (XXXVll) reacts approximately twenty times slower than the corresponding oxygen compound (XXXVlll).



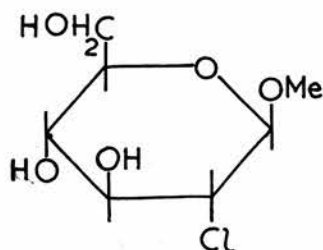
(XXXVll)



(XXXVlll)

In the acyclic series, Böhme compared the reactivities of alkyl 1-chloromethyl ethers and sulphides, and found the first-order solvolysis of the sulphides to be much slower (cf. p. 37). The results would appear to establish that in these reactions, the hetero-atom is responsible for the ease of nucleophilic displacement of the halogen because of its ability to release electrons to the seat of substitution. Further support for this is evident in the inertness of the halogen atom when it is not part

of the α -halogeno system. Thus even after heating with methanol at 98° for 500 hours, methyl 2-chloro-2-deoxy- β -D-glucoside (XXXIX) and its 3,4,6-triacetate were recovered unchanged⁽¹⁰⁰⁾.



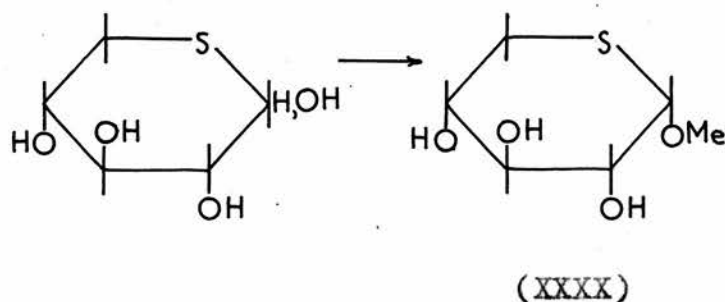
(XXXIX)

Apart from the difference in the reaction rates of methanol with 2,3,4-tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranosyl bromide and its oxygen analogue, the other main difference is the configuration of the reaction products. From the final rotation value it was calculated that in the case of the oxygen sugar, the product was almost completely methyl β -xylopyranoside triacetate, and this was confirmed chromatographically. The final rotation of the methanolysis solution of the thiosugar (cf. p. 69) however, indicated that the main product (ca. 60%) was methyl 2,3,4-tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranoside. Also, when the partially deacetylated product was reacetylated, the methyl α -triacetate was shown (chromatographically) to predominate. A tentative explanation for these results has already been offered (cf. p. 67).

Section 111 : Preparation and Hydrolysis of Methyl 5-deoxy-5-thio- α - and β -D-xylopyranosides.

(i) Preparation of methyl 5-deoxy-5-thio- α - and β -D-xylopyranosides.

Methyl 5-deoxy-5-thio- α -D-xylopyranoside (XXXX) was obtained by the direct Fischer method⁽¹⁰¹⁾, by refluxing 5-deoxy-5-thio-D-xylopyranose with methanolic hydrogen chloride (0.5N) for 6 hours. Paper and cellulose column

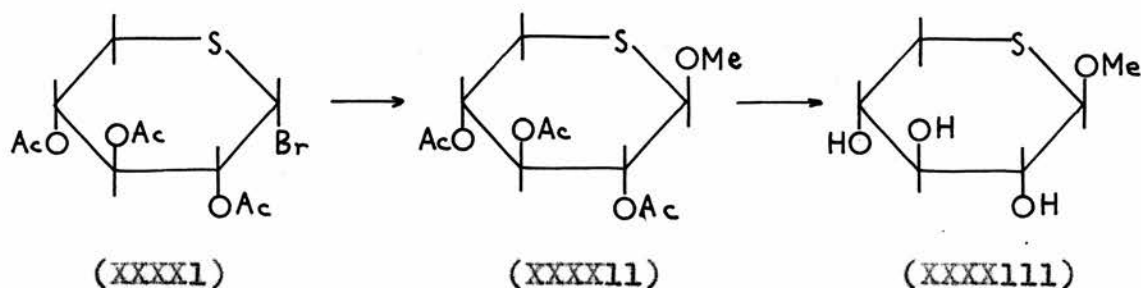


chromatography (methyl ethyl ketone/water : 10/1) showed that the product was mainly the α -glycopyranoside, but in addition there was ca. 5% of a faster moving substance. Initially it was thought that this compound could be a furanoside, but tests with dichlorophenol indophenol (cf. p. 50) and with sodium nitroprusside and alcoholic sodium hydroxide failed to show the presence of a free -SH group. The compound was not identified.

No direct chromatographic evidence was obtained regarding the presence of β -glycopyranoside; however, when the crude product of the reaction was acetylated a little methyl β -triacetate was shown to be present. From the rotation of the pure α - and β -glycopyranosides and the

rotation of the pyranoside fraction obtained by cellulose column chromatography of the crude glycosides, it was calculated that the α/β ratio was about 9/1. Bishop⁽¹⁰²⁾ has shown that when D-xylopyranose is refluxed for twenty hours in methanolic hydrogen chloride (2%), the product consisted of α -pyranoside (60%), β -pyranoside (32%), β -furanoside (6.5%) and α -furanoside (1.4%).

The methyl β -glycoside (XXXX111) was prepared indirectly by sodium methoxide deacetylation of the β -methyltriacetate (XXXX11), prepared from the corresponding acetobromo-compound (XXXX1) by the Koenigs-Knorr reaction. The β -glycoside absorbed water from the atmosphere to form a hemi-hydrate,



which could be dehydrated back to the glycoside on heating at 40° in vacuo.

(ii) The kinetics of the acid hydrolysis of the methyl 5-deoxy-5-thio-D-xylopyranosides,

(a) Preliminary considerations.

Since both methyl glycopyranosides of the thiosugar were available, it seemed of interest to compare the rates of hydrolysis of these compounds with those of the

methyl xylosides. In particular, it was hoped that the results might provide additional evidence about the mechanism of glycoside hydrolysis.

In order to decide on the best conditions (temperature and acidity) for the hydrolysis of the methyl glycosides of the thiosugar a trial experiment was carried out, in which the hydrolysis of methyl 5-deoxy-5-thio- α -D-xylopyranoside with hydrochloric acid (2N) at 60° was followed polarimetrically. Two observations caused a certain amount of surprise. Firstly, the hydrolysis was faster than that of the corresponding oxygen compound, and secondly the final specific rotation of the solution differed greatly from +178°, the equilibrium value for the mutarotation of 5-deoxy-5-thio-D-xylopyranose. In fact, the observed rotation fell steadily reaching, after thirty hours, a value $[\alpha]_D +15^\circ$; thereafter, the solution became too discoloured for polarimetric observation. After two days the experiment was discontinued and 2-thiophenylaldehyde was shown to be present in the solution by isolation of the p-nitro-phenylhydrazone. The weight of this derivative indicated that the amount of thiophenylaldehyde present was ca. 50% of the theoretical.

In view of the results of the trial hydrolysis, it seemed unlikely that polarimetric observation of the rate of hydrolysis would provide rate constants with sufficient accuracy to permit the calculation of activation energies. We therefore turned to the possibility of following the

hydrolysis by estimating the liberated methanol. This method has been successfully used by D.B. Easty for the hydrolysis of methyl α -D-glucopyranosiduronic acid⁽¹⁰³⁾, the methanol being distilled out of the neutralised hydrolysate and oxidised with permanganate to formaldehyde, which was then estimated spectrophotometrically with chromotropic acid⁽¹⁰⁴⁾.

However, experiments with standard solutions showed that thiophenalddehyde interfered with the estimation of methanol by the above method (curiously, the presence of thiophenalddehyde led to higher results in the methanol estimation than could be accounted for by the separate absorbance due to the thiophenalddehyde). Although it seemed possible, in theory, to devise a method for removing the thiophenalddehyde prior to oxidation of the methanol, it was considered that this would make the method too cumbersome and the possibility of estimating the methanol by gas-liquid chromatography was therefore investigated.

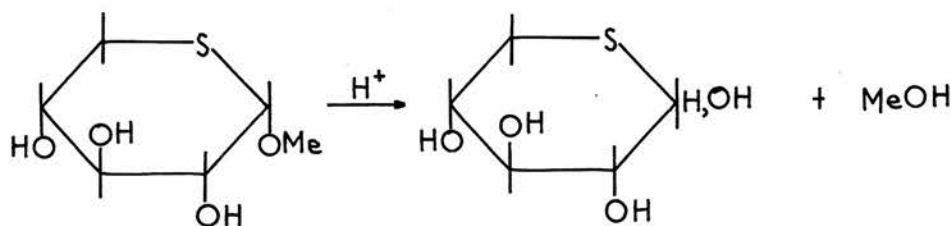
(b) Estimation of methanol by gas-liquid chromatography.

Although the estimation of alcohols in dilute aqueous solutions by gas-liquid chromatography has been described in the literature, considerable time and effort were required before the apparatus and technique were perfected sufficiently to provide the precision of 1%, desired for the methanol estimations. The apparatus is described in full in the Experimental. Essentially it consisted of a

sample volatiliser, a polyethylene glycol-celite column, a flame-ionisation detector, an amplifier and a recorder. All except the last two were constructed in the Department. A flame-ionisation detector was used since this is insensitive to water.

It was decided that a convenient way to analyse a solution for methanol would be to have present in the solution a standard quantity of n-propyl alcohol, with which the variable quantity of methanol could be compared. This avoided the problem of measuring accurately the small volume of solution (ca. 0.003 ml.) used in the G.L.C. analysis. The first experiments therefore, involved the variation of the column packing, the nitrogen carrier-gas flow rate, the hydrogen flow rate, the size of the sample injected, the amplification of the signal received from the flame-ionisation detector and the design of a suitable sample volatiliser, among other things, until finally we were able to determine the ratio of methanol and n-propanol in an aqueous solution with a reproducibility better than $\pm 1\%$. We then turned to the specific problem in hand.

We wished to follow the production of methanol when a 1% solution of e.g. methyl 5-deoxy-5-thio- α -D-xylopyranoside was hydrolysed with dilute acid, thus :



From the above equation it is seen that 32g. of methanol are produced from 180g. of glycoside, and it follows that during the reaction, the methanol content varies from 0 to 1778 parts per million for a 1% solution of the glycoside. Preparation and G.L.C. analysis of four standard solutions (of known methanol content covering the range 80 \rightarrow 450p.p.m. and containing a standard quantity of n-propanol) showed that the ratio of the peak heights of the two alcohols was a linear function of the methanol concentration over the above range. It was also shown that a standard solution of methanol and n-propanol in 0.2N hydrochloric acid was stable over three days at 80°.

(c) Kinetic procedure and results.

On the basis of the preliminary experiment it was decided that hydrolysis with 0.2N hydrochloric acid would give rate constants of convenient magnitude. Hydrolysis was therefore carried out at this concentration of acid; full details of the experimental technique, which involved the use of sealed ampoules, are given in the Experimental. n-Propanol was added as internal standard and after neutralisation the reaction solutions were analysed by gas-liquid chromatography by reference to a standard methanol-n-propanol solution. Details of a typical run are given in the Experimental.

Theoretical considerations⁽¹⁰⁵⁾ indicate that in a first-order reaction which is followed by the analysis of

a product, the early stages of the reaction yield the most accurate rate constants. In general, therefore, the rate constants were calculated from analyses covering only the first half-life. However a further analysis was carried out after ca. two half-lives since this provides a more sensitive check on the order of the reaction. Finally, an analysis was carried out after completion of the hydrolysis (> ten half-lives). Good first-order plots were obtained and the methanol content of the final solutions was within 1% of the value expected from the quantity of glycoside used.

Hydrolysis rates for both thioglycosides were determined in duplicate at three convenient temperatures; the results are given in Table 26. In addition, the rate of hydrolysis of methyl β -D-xylopyranoside in hydrochloric acid (0.2N) was measured at 79.9°. Calculation of the rate of hydrolysis of this compound in hydrochloric acid (0.2N) at 79.9°, from the data obtained by Overend, Rees and Sequeira⁽¹⁰⁶⁾ who used 2N hydrochloric acid at 79.9°, gives $k = 4.80 \times 10^{-5}$. The discrepancy is perhaps not surprising since the calculation is based on H_0 values obtained at 25°⁽¹⁰⁷⁾.

Energies and entropies of activation were calculated for each of the thioglycosides (cf. ref. 106) and the values may be compared with those obtained by Overend et al for the oxygen analogues (see Table 26).

Table 26. Rate coefficients and kinetic parameters for the hydrolysis of glycosides in 0.2N hydrochloric acid.

<u>Pyranosides</u>	<u>Temp.</u> (°C)	<u>Rate Const.</u> $k \times 10^5$ (sec. ⁻¹)	<u>E</u> (k cal. mol. ⁻¹)	<u>ΔS at 60</u> cal. deg. ⁻¹ mol. ⁻¹
Methyl 5-deoxy-	60.0	1.906		
5-thio- α -D-xylo-		1.869	29.76 ^a	
	69.9	6.956	29.83 ^b	
		6.876	<u>29.75</u> ^e	+ 9.94
	80.0	23.73		
		24.64		
Methyl 5-deoxy-	55.0	2.595		
5-thio- β -D-xylo-		2.561	30.26 ^c	
	65.0	10.18	28.39 ^d	
		10.18	<u>29.26</u> ^e	+ 10.44
	75.0	34.18		
		34.38		
	80.0	61.80		
	(extrapolated)			
Methyl β -D-xylo-	79.9	3.819	-	-
		3.831		
Methyl α -D-xylo- ^f	60.0	2.69	33.5	+ 15.7
Methyl β -D-xylo- ^f	60.0	5.89	33.6	+ 17.5

a,b,c etc. see over.

a, b, c and d were calculated from the expression

$$\log \frac{k_2}{k_1} = \frac{E}{2.303R} \cdot \frac{T_2 - T_1}{T_1 T_2} \quad \text{where} \quad T_1(^{\circ}\text{K}) ; T_2(^{\circ}\text{K})$$

a	333	342.9
b	342.9	353
c	328	338
d	338	348

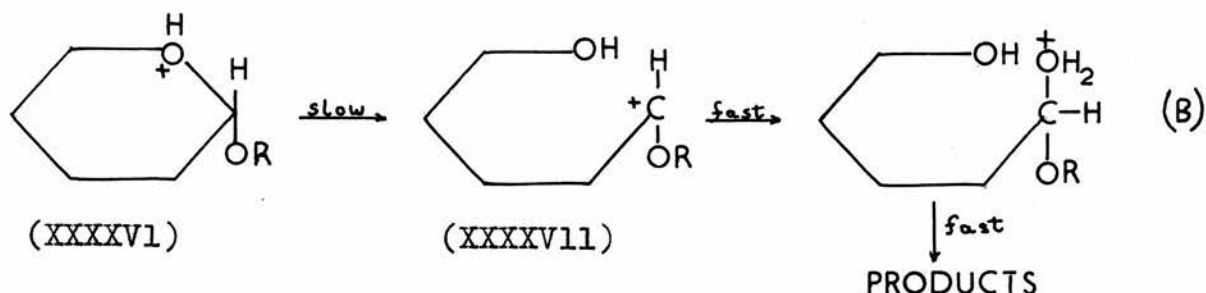
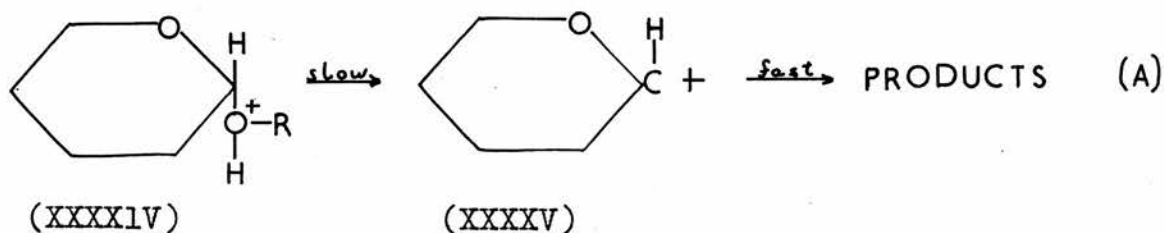
e: Calculated from the slope of the plot $\log k$ against $\frac{1}{T}$ (abs.)

f: Hydrolysis with 2.0N hydrochloric acid⁽¹⁰⁶⁾.

(d) Discussion of the kinetic results.

The hydrolysis of glycosides is generally considered to take place by either of two mechanisms. According to Bunton and co-workers⁽¹⁰⁸⁾ the hydrolysis of methyl and phenyl α - and β -D-glycopyranosides proceeds through the unimolecular heterolysis of the glycoside conjugate acid with fission of the glycosyl-oxygen bond. They based these conclusions on the linear relationships found between the first-order rate constant and the Hammett acidity function⁽¹⁰⁹⁾. By isotopic tracer methods they showed that the hydrolysis of the above glycosides in an aqueous solution containing H_2O^{18} , provided unlabelled phenol and unlabelled methanol. From their results they consider that the rate-determining unimolecular step can be formulated in two ways : first,

the conjugate acid (XXXXIV) undergoes heterolysis to form the carbonium ion (XXXXV), subsequent reaction with water being rapid (Scheme A); or, secondly, the conjugate acid (XXXXVI) undergoes ring-opening between the oxygen and C₁ to form the ion (XXXXVII), subsequent rapid stages involving attack by a water molecule and loss of methanol or phenol.



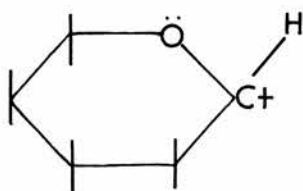
The evidence cited above for the unimolecularity of these hydrolyses has received additional support from a consideration of the magnitude of the entropy of activation for the hydrolysis of twenty-four pyranosides⁽¹⁰⁶⁾. Overend and co-workers found that all the glycopyranosides hydrolysed had positive entropies of activation, indicating a unimolecular mechanism⁽¹¹⁰⁾. Reactions of the A-1 type⁽¹¹¹⁾ have, relatively, a more positive entropy of activation than those

proceeding by an A-2 mechanism. The transition state for the latter is more ordered, owing to the specific orientation of a water molecule from the solvent. We have found that the entropies of activation for the hydrolysis of the methyl 5-deoxy-5-thio- α - and β -D-xylopyranosides are positive (+9.9 and +10.4 e.u. respectively), suggesting the mechanism of hydrolyses of these compounds is probably similar to that of the oxygen analogues. However, a positive entropy does not necessarily indicate a unimolecular mechanism⁽¹¹³⁾. In addition, the validity of the Zucker-Hammett hypothesis has been challenged by Withey and Whalley⁽¹¹²⁾ who, however, produce evidence in support of the unimolecularity of the mechanism, based on the effect of pressure on the hydrolysis of methyl α -D-glucopyranoside.

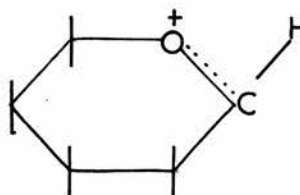
Of the two mechanisms A and B, the first mechanism A has been gaining increasing acceptance over the years^(106, 114, 115). Shafizadeh⁽¹¹⁶⁾ has summarised the evidence for mechanism B, but the circumstantial evidence he presents has been refuted⁽¹¹⁷⁾.

We have shown that the hydrolysis of methyl 5-deoxy-5-thio- β -D-xylopyranoside in 0.2N hydrochloric acid at 80° proceeds about sixteen times faster than that of methyl β -D-xyloside, and that the difference is due to a more favourable energy of activation, which in turn is probably due to an electronic effect (cf. ref. 103). A consideration of mechanism A, at first sight, makes our results seem surprising,

because it might be expected that the rate-determining production of the carbonium ion (XXXXV) would be more favourable for the oxygen compound because of the greater resonance stabilisation (XXXXV111) of an adjacent positive charge by oxygen than sulphur (cf. p. 38; also p.70 for discussion of the methanolysis of the corresponding acetobromides).

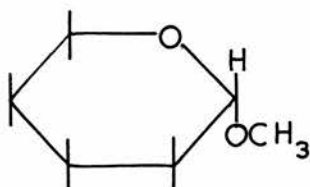


XXXXV

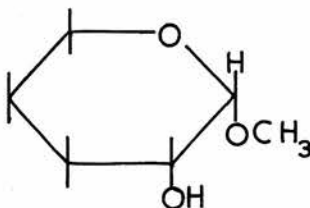


XXXXV111

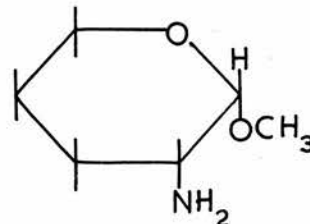
Some other factor therefore, must be responsible and it is considered that the difference in rates must be caused by the smaller inductive effect of sulphur than oxygen, which allows correspondingly greater initial protonation of the oxygen of the methoxyl group. A similar consideration^(118, 119, 106) has been put forward to explain the influence of the substituent on C-2. Thus, of the three types of methyl glycopyranosides represented as 1L, L and L1 only the 2-deoxy glycoside 1L is hydrolysed at the rate for a normal aliphatic acetal; the hydrolysis of a glycoside of a normal sugar (L)



1L



L



L1

proceeds about one thousand times slower, protonation being decreased by the -I effect of the hydroxyl group. The hydrolysis of the glycoside of an amino sugar (L1) is much slower still, since the presence of the $-\text{NH}_3^+$ group strongly suppresses further protonation⁽¹²⁰⁾.

The hydrolysis of the 5-deoxy-5-thioglycosides must almost certainly proceed by mechanism A, since protonation of the sulphur is highly unfavoured (as confirmed by the mutarotation experiments). Further, the fact that ethyl 1-thio- β -D-glucopyranoside is hydrolysed more slowly than its oxygen analogue⁽¹¹⁵⁾ provides additional evidence that ordinary pyranosides react by mechanism A since our results suggest that if mechanism B operated, the sulphur analogue should react more quickly owing to increased protonation.

We have also shown that the β -glycoside of the thio-sugar is hydrolysed at 60° about 2.7 times faster than the α -glycoside; this compares with a similar ratio of 2.2 for the hydrolysis (2.0N hydrochloric acid at 60°) of the methyl D-xylopyranosides. As was mentioned earlier (p.60), the greater reactivity of the β -anomers has been ascribed by Edward⁽⁷⁷⁾ to their higher free energy in the ground state, caused by polar interaction between the equatorial methoxyl group and the lone pairs of electrons of the ring-oxygen atom. It has been pointed out⁽¹⁰⁶⁾ that this repulsive interaction will be destroyed on protonation, and the difference in rate may be related to a higher concentration of the

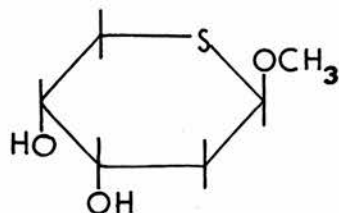
equatorial β -conjugate acid.

(iii) Relative acidities of methyl 5-deoxy-5-thio- α - and β -D-xylopyranosides.

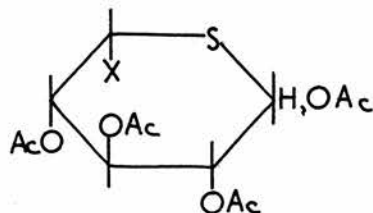
Mr. J.C. Clapperton of this Department has kindly examined the electrophoretic mobilities of the methyl glycosides of the thiosugar and its oxygen analogues in sodium hydroxide (0.5N) on glass-fibre paper; these mobilities provide a measure of the relative acidities of the compounds. For both the α - and β -methyl glycosides, the sulphur compound appears to be less acidic than the oxygen compound, as would be expected from the smaller -I effect of sulphur (cf. p.40). However, methyl 5-deoxy-5-thio- β -D-ribose, kindly provided by Dr. N.A. Hughes⁽¹²¹⁾, was found to migrate at the same rate as methyl β -D-ribose; explanation of this discrepancy will require a more thorough understanding of the various factors which influence the acidity of the hydroxyl groups of glycosides.

Section 1V : Other work on Sugars with Sulphur in the Ring.

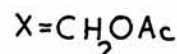
Sugars with "sulphur in the ring" were not reported in the literature before our own publication in November 1961, but within a year, reports from four independent laboratories described such sugars^(4,59,72,121). Each synthesis involved the preparation of a 5-thio derivative, which cyclised under acid conditions to give a compound with sulphur in the ring. Among the synthesis reported, and not already mentioned in this thesis, was that of 5-deoxy-5-thio-D-ribopyranose by Clayton and Hughes⁽¹²¹⁾, whose route was essentially the same as that used by Adley and Owen⁽⁵⁹⁾ to synthesise the corresponding xylose compound (cf. p.48). The synthesis of methyl 2,5-dideoxy-5-thio-β-D-ribopyranose (L11) has also been described⁽¹²²⁾.



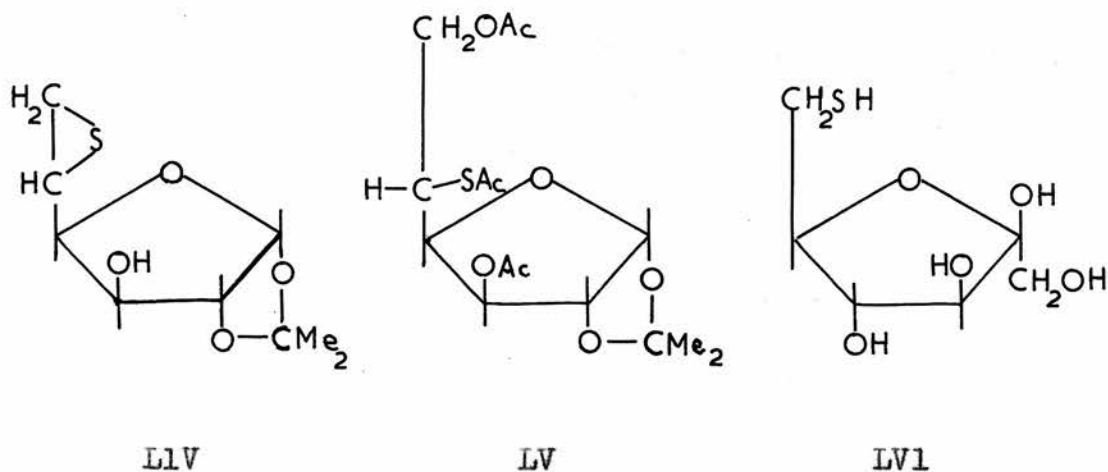
L11



L111

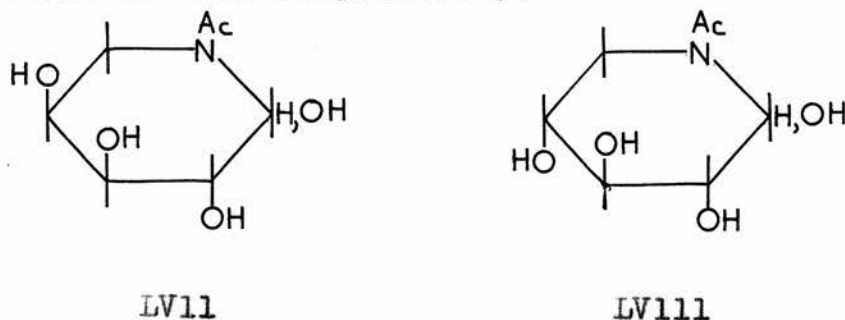


In their original publication⁽⁵⁹⁾, Adley and Owen also described the preparation of a hexose derivative, namely, the penta-acetate of 5-thio-L-idopyranose (L111). The synthesis was achieved by opening the ring of 5,6-dideoxy-5,6-epithio-1,2-O-isopropylidene-L-idofuranose⁽¹²³⁾ (L1V) with acetic anhydride-acetic acid-potassium acetate



at 130° to give 3,6-di-O-acetyl-5-acetylthio-5-deoxy-1,2-O-isopropylidene-L-idofuranose (LV), which, after acid hydrolysis followed by acetylation, gave (L111). Using a closely similar route, Whistler and Feather succeeded in preparing a penta-acetate and a methyl glycoside of 5-deoxy-5-thio-D-glucopyranose⁽¹²⁴⁾. They have also prepared^(124a) 6-deoxy-6-mercapto-D-fructose (LV1) and presented evidence based on IR spectroscopy that this sugar exists with sulphur in the pyranose ring.

As well as these examples of sulphur-ring sugars, the selenium analogue of methyl 5-deoxy-5-thio- α -D-xylopyranoside has also been prepared⁽¹²⁵⁾. Recently other interesting examples of sugars containing nitrogen as the hetero atom in the ring have been described. J.K.N. Jones and J.C. Turner⁽¹²⁶⁾ and J.K.N. Jones and W.A. Szarek⁽¹²⁷⁾ have synthesised an L-arabinose derivative (LV11) and a D-xylose derivative (LV111) respectively.



After the completion of the previous sections of this thesis, Whistler and Van Es published⁽¹²⁸⁾ the results of work on the methanolysis of 2,3,4-tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranosyl bromide and the corresponding oxygen compound; their results and their interpretation of their results are in agreement with those recorded in this thesis. They made no mention of any complications due to deacetylation (cf. p.68). In the same paper they also report the results of the acid hydrolysis (hydrochloric acid, 0.5N at 75°) of the methyl 5-deoxy-5-thio- α - and β -D-xylopyranosides; again our results and theirs are in general agreement. Their hydrolysis rates were observed polarimetrically and in view of the decomposition witnessed in our hydrolysis experiment (hydrochloric acid, 2.0N at 60°) with the α -anomer, their results may not be entirely accurate. Whistler and Van Es consider that "the high rate of hydrolysis of the thioglycosides can be explained by the high concentration of its conjugate acid, due to the inductive effect of the sulphur-releasing electrons to the exocyclic oxygen". Perhaps this would be better expressed as the lesser tendency of sulphur than oxygen to withdraw electrons from the exocyclic oxygen, the potential seat of protonation (cf. p.83). Again, they consider that "the ring oxygen of normal D-xylopyranosides probably undergoes competitive protonation with the exocyclic oxygen, thus decreasing the amount of conjugate acid effective in the

hydrolysis". We consider that this argument is unsound since the total extent of protonation is small (cf. ref. 77).

EXPERIMENTAL

Section I : General Information on Experimental Procedures.

(i) Optical rotations were measured in a variety of 1 dm. and 0.5 dm. tubes (1 ml., 5 ml., and 10 ml.). The infrared spectra were obtained using a Perkin-Elmer Model 137 Infracord spectrophotometer and the ultraviolet spectra using a Unicam SP 500 spectrophotometer. The light petroleum used had a boiling range 60-80°. Evaporations were carried out under reduced pressure at temperatures below 40°, generally on a rotatory evaporator, unless otherwise stated.

(ii) Whatman No. 1 paper was used for the paper chromatograms (descending) and the solvent systems used were :

- A - n-butanol - ethanol - water (4:1:5, upper layer)
- B - n-butanol - pyridine - water (10:3:3, upper layer)
- C - methyl ethyl ketone - Water (10:1)
- D - dimethyl sulphoxide as stationary phase and di-isopropyl ether as mobile phase. The procedure of Wickberg⁽⁶⁶⁾ was used, except that after application of the dimethyl sulphoxide as a solution (25% v/v) in toluene, the papers were heated at ca. 80° for 1 min., instead of at 60°.

Sprays used were :

- a - a solution (ca. 1%) of aniline oxalate or phthalate in

water, followed by heating at 120° for 15 min.

b - an ethanolic solution of sodium hydroxide (0.5N)

preceded by passage of the paper through a solution of silver nitrate (2%) in acetone containing the minimum of water. The paper was left between glass sheets while the spots developed (ca. 5 min.); it was "fixed" by passing through a solution of sodium thiosulphate (10%).

c - as in (b), but aqueous silver nitrate (2%) was used.

It was unnecessary to place the paper between glass sheets.

d - an ethanolic solution of sodium hydroxide (0.5N). The paper was allowed to dry for a minute, and then sprayed with an aqueous solution (1%) of sodium nitroprusside.

Section II : Preparations.

(i) 1,2; 3,5-Di-O-isopropylidene-D-xylofuranose.

1,2; 3,5-Di-O-isopropylidene-D-xylofuranose was prepared by the method of Müller and Reichstein⁽⁵⁷⁾, but finely powdered calcium hydroxide was used, in place of potassium hydroxide, to neutralise the sulphuric acid. Crude yield : 88%.

(ii) 1,2-O-Isopropylidene-D-xylofuranose.

1,2-O-Isopropylidene-D-xylofuranose was prepared from the di-acetone compound (undistilled), by the method of Helferich and Burgdorf⁽⁵⁶⁾. The crude product was distilled at 0.7 mm., and the fraction boiling between 130-140° collected. Yield : 86%.

(iii) 1,2-O-Isopropylidene-D-xylofuranose 5-toluene-p-sulphonate.

1,2-O-Isopropylidene-D-xylofuranose 5-toluene-p-sulphonate was prepared by the method of Müller and Reichstein⁽⁵⁷⁾ (commercial pyridene, purified by boiling with potassium permanganate, dried and distilled over barium oxide, was used in place of chloroform)..The product was crystallised from chloroform/light petroleum; yield : 76%; m.p. 136-7°.

(iv) 5-Deoxy-1,2-O-isopropylidene-D-xylofuranose 5-thiocyanate.

1,2-O-Isopropylidene-D-xylofuranose 5-toluenesulphonate (4 g.) was added to a eutectic melt of sodium thiocyanate (13.17g., 30 mol.%) and potassium thiocyanate (36.83g., 70 mol.%) and the mixture stirred at 135° for 30 min. The melt was allowed to cool to room temperature, taken up in warm water (100 ml.) and filtered. The filtrate was extracted several times with chloroform and the combined extracts were, in turn, treated with animal charcoal, dried over sodium sulphate and evaporated to dryness. The crude product was crystallised from chloroform/light petroleum. Yield : 1.66g. (66%); m.p. 109.5-110.5°. The material was shown to be identical to that prepared by Schwarz⁽⁶⁰⁾ who heated the 5-tosylate with sodium thiocyanate in acetone in a sealed tube at 120°.

(v) 5-Deoxy-1,2-O-isopropylidene-D-xylofuranose 5-(mono-sodium thiosulphate).

1,2-O-Isopropylidene-D-xylofuranose 5-toluenesulphonate (20g.), sodium thiosulphate (hydrated, 43g., 2 molar proportions), dimethyl formamide (100 ml.) and water (100 ml.) were gently refluxed for four hours. The resulting mixture was evaporated (in vacuo at 50°), water added and the evaporation repeated; this procedure was repeated until the bulk of the dimethyl formamide was removed. The residue was

taken up in water (200 ml.) and extracted twice with chloroform. The chloroform extract yielded unreacted 5-toluene-sulphonate (5%); the aqueous layer was concentrated and treated as below.

(vi) 5-Deoxy-1,2-O-isopropylidene-D-xylofuranose 5-thiol.

(a) By reduction of the 5-Bunte salt.

To the solution of the above Bunte salt dissolved in water (100 ml.) and alcohol (100 ml.) was added potassium borohydride (4.8g., 3 molar proportions) dissolved in water (40 ml.) over a period of 30 min. Vigorous effervescence accompanied each addition of reducing agent. The mixture was allowed to stand for a further 30 min., and then evaporated to dryness. Water (250 ml.) was added to the residue and the resulting mixture was filtered to remove the disulphide; the filtrate was then extracted four times with chloroform and the combined extracts dried and evaporated, (the quantity of disulphide removed was 2.6g.; m.p. 176-9°). The product was sublimed twice at ca. 100° and 0.2 mm. pressure. The sublimate was 5-deoxy-1,2-O-isopropylidene-D-xylofuranose 5-thiol and was identical with a sample prepared by Schwarz⁽⁶⁰⁾ by the reduction of the 5-thiocyanate with sodium sulphide. Yield : 9.0g. (74%); m.p. 85-86°; $[\alpha]_D^{20} - 52^\circ$ (c 1.0 in chloroform).

(b) By reduction of the 5-thiocyanate.

Potassium borohydride (0.7g., 3 molar proportions) dissolved in water (5 ml.) was added to a solution of 5-deoxy-1,2-O-isopropylidene-D-xylofuranose 5-thiocyanate (2g.) in aqueous alcohol (16 ml., 1:1) at 40°. Immediate effervescence and evolution of hydrogen cyanide followed. The reaction mixture was allowed to stand for one hour and then worked up as described above. Yield of sublimed 5-thiol : 0.57g. (32%). Paper chromatography (Solvent A, spray a, R_F 0.84).

(c) By the reduction of the 5-disulphide.

Bis(5-deoxy-1,2-O-isopropylidene-D-xylofuranose) 5,5'-disulphide (8g.) was suspended in anhydrous ether (150 ml.), lithium aluminium hydride (8.5g.) in ether (40 ml.) added, and the mixture left for 1 hour at room temperature. Excess reducing agent was destroyed with water and hydrochloric acid, and the ether layer separated. Concentration of the ether solution gave the crude product (6.8g.). This was sublimed at ca. 100° and 0.2mm. pressure. Yield : 4.5g. (56%).

(vii) Bis(5-deoxy-1,2-O-isopropylidene-D-xylofuranose) 5,5'-disulphide.

(a) By oxidation of the 5-thiol with iodine.

Iodine (0.62g.) dissolved in potassium iodide solution (5 ml., 20%) was added dropwise to a solution of 5-deoxy-1,2-O-isopropylidene-D-xylofuranose 5-thiol (1g.)

in aqueous alcohol (10 ml., 1:1); decolourisation of the iodine solution was immediate. The slight excess of iodine was removed with sodium thiosulphate. The product was extracted with chloroform and the combined extracts evaporated to dryness. The resulting solid was identified as bis(5-deoxy-1,2-O-isopropylidene-D-xylofuranose) 5,5'-disulphide (m.p. 177-8°), identical to a sample prepared by Schwarz⁽⁶⁰⁾, who treated the 5-thiocyanate with sodium hydroxide.

In a similar experiment, the 5-thiol (0.010g.) was dissolved in potassium hydrogen phthalate solution (0.005N) and titrated with iodine solution (0.0102N). Titre : 4.77 ml.; calculated titre : 5.11 ml.

(b) By oxidation of the Bunte salt with iodine.

The 5-(monosodium thiosulphate) i.e. the Bunte salt was prepared as described above (cf. p.93) from the 5-toluene-*p*-sulphonate (1g.), and the dimethyl formamide removed in vacuo. To the Bunte salt dissolved in water (50 ml.) was added a solution of iodine (0.72g.) in potassium iodide solution (10%, 10ml.). After 30 min. the excess of iodine was reacted with sodium thiosulphate and the mixture extracted with chloroform. The product of the reaction was obtained by evaporating the chloroform extracts, and it was identified as bis(5-deoxy-1,2-O-isopropylidene-D-xylofuranose) 5,5'-disulphide. Yield : 0.3g. (50%).

(viii) 5-Deoxy-5-thio- α -D-xylopyranose.

(a) Using Amberlite IR 120 resin.

5-Deoxy-1,2-O-isopropylidene-D-xylofuranose 5-thiol, (10g.), which had been twice sublimed, water (800 ml.) and Amberlite resin (IR 120, H⁺ form, 180g.) were shaken together for three days. The resin was filtered off, washed with water and the combined filtrate and washings evaporated. The product was chromatographically pure (Solvent A, spray a, R_F 0.31; Solvent B, spray a, R_F 0.44), and the "crude" yield practically quantitative. The product was dissolved in the minimum of hot water, absolute alcohol (25 ml.) added, a very small flocculent precipitate filtered off, and the solution allowed to crystallise. A second, a third crop (etc.) of crystals were obtained by evaporating the filtrate and repeating the above procedure, m.p. 122-124°, $[\alpha]_D^{20} +202^\circ \rightarrow +178^\circ$ (c 2 in water). (Found : C, 35.9; H, 5.9; S, 19.9. C₅H₁₀O₄S requires C, 36.2; H, 6.0; S, 19.3%).

(b) Using sulphuric acid (0.1N).

5-Deoxy-1,2-O-isopropylidene-D-xylofuranose 5-thiol (0.5g.) was dissolved in dilute sulphuric acid (15 ml., 0.1N) at 78° and the solution observed polarimetrically. After two hours the rotation had reached a constant value. The solution was then cooled, made slightly alkaline with barium hydroxide solution, the excess alkali neutralised with carbon

dioxide and the mixture filtered. The crude product was run on a paper chromatogram (Solvent B, spray a) and shown to consist largely of 5-deoxy-5-thio-D-xylopyranose (R_F 0.44), together with a little of a slower moving compound (R_F 0.28). The crude sugar was recrystallised as detailed above (a).

(ix) Bis(5-deoxy-D-xylofuranose) 5,5'-disulphide.

Bis(5-deoxy-1,2-O-isopropylidene-D-xylofuranose) 5,5'-disulphide (lg.) was shaken with sulphuric acid (30 ml., 0.1N) for one hour at 80° , during which time it completely dissolved. The solution was made slightly alkaline with barium hydroxide solution and then neutralised with carbon dioxide. The precipitated barium salts were filtered off and the filtrate evaporated. The crude disulphide was crystallised three times from aqueous alcohol (1 : 1), m.p. $169-175^\circ$ (decomposition); $[\alpha]_D^{20} +119^\circ$ (c 0.8 in water). (Found : C, 36.4; H, 5.3; S, 19.5; $C_{10}H_{18}O_8S_2$ requires C, 36.3; H, 5.5; S, 19.4%). The pure disulphide was run on a paper chromatogram (Solvent A, spray a, R_F 0.3); (solvent B, spray a, R_F 0.55).

(x) 1,2,3,4-Tetra-O-acetyl-5-deoxy-5-thio- α - and β -D-xylopyranoses.

(a) Using acetic anhydride/sodium acetate.

5-Deoxy-5-thio-D-xylopyranose (1.5g.) was added in

ten portions, over an hour, to a mixture of sodium acetate (anhydrous, 0.75g.) and acetic anhydride (9 ml.) at 100° , and the mixture maintained at 100° for a further hour. Only a little darkening of the solution occurred. The mixture was cooled, poured with stirring into ice-water (25 ml.) and extracted with chloroform several times. The combined chloroform extracts were washed twice with water, dried and evaporated.

The crude product (2.8g.), $[\alpha]_D +170^{\circ}$ (c 3.0 in chloroform), was crystallised from aqueous alcohol (90%; 15ml.) to give a first fraction, further crystallisation of which (90% alcohol) yielded pure 1,2,3,4-tetra-O-acetyl-5-deoxy-5-thio- β -D-xylopyranose, (0.27g, 9%), $[\alpha]_D -49^{\circ}$ (c 2.3 in chloroform); m.p. $157-158.5^{\circ}$. (Found : C, 46.5; H, 5.6; S, 9.5. $C_{13}H_{18}O_8S$ requires C, 46.7; H, 5.4; S, 9.6%).

Another crop of crystals was obtained from the mother liquor after partial evaporation; further crystallisation (90% alcohol) of the crystals gave the corresponding α -anomer (0.5g., 17%), $[\alpha]_D^{20} +219^{\circ}$ (c 2.2 in chloroform); m.p. $99-100^{\circ}$. (Found : C, 46.5; H, 5.5; S, 9.7%).

(b) Using acetic anhydride/pyridine.

5-Deoxy-5-thio-D-xylopyranose (1g.) was added to a cold mixture (0°) of pyridine (12 ml.) and acetic anhydride (5 ml.). The ice-bath, in which the mixture was cooled, was

allowed to come to room temperature overnight. The mixture was then poured with stirring into ice-water (25 ml.).

The precipitate formed, was filtered off and washed several times with water. The crude product, yield : 1.9g. (95%), was crystallised from aqueous alcohol (80%) to give the α -anomer : 1.5g. (75%). Paper chromatography (Solvent D, spray c) of the crude product showed that the β -anomer was also present (α : R_F 0.43; β : R_F 0.17).

(c) By the reaction of silver acetate on the acetohalo sugar.

2,3,4-Tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranosyl 1-bromide (0.4g.) was dissolved in glacial acetic acid (8 ml.) and shaken with silver acetate (0.5g.) for 90 min. The mixture was filtered, and the filtrate diluted with water, neutralised with sodium bicarbonate and extracted with chloroform. The chloroform extract was concentrated to a thick syrup (0.38g.), $[\alpha]_D + 60^\circ$ (c 0.8 in chloroform). The crude product was crystallised from absolute ethanol to yield the β -tetra-acetate (0.1g., ca. 25%).

The α -tetra-acetate was also present in the reaction product, as evidenced by paper chromatography (Solvent D, spray c).

(d) UV and IR spectra of the tetra-acetates.

UV Spectra - Approximately 0.001M solutions of the anomeric tetra-acetates were prepared in spectroscopic ethanol . The optical density of each solution was measured spectroscopically in a stoppered silica cell (1 x 1 cm.), in conjunction with a blank solution of ethanol. The results are tabulated below (Tables 27, 28).

IR Spectra - Both the anomeric acetates showed a strong absorption peak at 1750 cm.^{-1} , attributable to the C=O stretching vibration absorption of normal saturated esters. Neither acetate exhibited the characteristic absorption at 1675 cm.^{-1} , for the C=O stretching vibrations in a thioester.

Table 27. UV spectra of 1,2,3,4-tetra-O-acetyl-5-deoxy-5-thio- α -D-xylopyranose.

$\lambda(\text{m}\mu)$	ϵ	$\lambda(\text{m}\mu)$	ϵ
280	2	215	277
270	1	212	289
260	2	210	294
250	10	208	288
240	38	206	275
230	110	204	241
220	233	202	194
218	253		

Table 28. UV spectra of 1,2,3,4-tetra-O-acetyl-5-deoxy-5-thio- β -D-xylopyranose.

$\lambda(\text{m}\mu)$	ϵ	$\lambda(\text{m}\mu)$	ϵ
280	0	220	260
270	0	215	285
260	3	212	289
250	18	210	289
245	39	208	284
240	70	206	289
235	111	204	288
230	165	202	263
225	213	200	141

(xi) 2,3,4-Tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranosyl
1-bromide.

1,2,3,4-Tetra-O-acetyl-5-deoxy-5-thio-D-xylopyranose (2.0g.), prepared as in x(b), was dissolved in glacial acetic acid (5 ml.) and to this solution was added hydrogen bromide in acetic acid (50% w/v; 10 ml.). After 30 min. at room temperature, the mixture was poured into alcohol-free chloroform, extracted twice with ice-water, once with iced sodium bicarbonate solution, once with ice-water and then dried over sodium sulphate. After evaporation of the chloroform, the crude product was dissolved in anhydrous ether, and passed through a column of silica gel (B.D.H., chromatographic grade)⁽¹²⁹⁾. The pure product was obtained by evaporation of the ether, $[\alpha]_D +240^\circ$ (c 1.5 in chloroform); m.p. 112-113°, yield : 1.8g.(85%). (Found : C, 37.3; H, 4.2; S, 9.1; Br, 22.5. $C_{11}H_{15}BrO_6S$ requires C, 37.2; H, 4.3; S, 9.0; Br, 22.5%).

(xii) Methyl 2,3,4-tri-O-acetyl-5-deoxy-5-thio- α - and β -D-xylopyranosides.

2,3,4-Tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranosyl 1-bromide (0.9g.) was dissolved in dry methanol (10 ml.) and shaken up with finely powdered silver carbonate (0.9g.) and a little Drierite ($CaSO_4$) for 24 hours. The mixture was filtered, and the silver carbonate washed with ether;

a little water was added to the combined filtrates and this solution treated with a small amount of barium carbonate. After filtration, the solution was evaporated, the product taken up in ether, and the ethereal solution extracted with sodium carbonate solution, then water, and finally dried over sodium sulphate. After evaporation, the reaction product was crystallised from 90% ethanol to yield methyl 2,3,4-tri-O-acetyl-5-deoxy-5-thio- β -D-xylopyranoside, yield : 0.24g.(31%), $[\alpha]_D -74^\circ$ (c 1.2 in chloroform); m.p. 119° . (Found : C, 47.1; H, 5.8; S, 9.3; $C_{12}H_{18}O_7S$ requires C, 47.0; H, 5.9; S, 10.5%).

The other product of this reaction, namely, methyl 2,3,4-tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranoside, was isolated by column chromatography (see below) in only minute yield. It was identified chromatographically, and by mixed melting point, with a sample of the α -isomer prepared by the acetylation of methyl 5-deoxy-5-thio- α -D-xylopyranoside (0.2g.) with acetic anhydride (1 ml.) in pyridine (1.5 ml.) at 0° . The product of the latter reaction was worked up as in the acetylation of 5-deoxy-5-thio-D-xylopyranose (see p.99) and crystallised from ether/light petroleum after several days, yield : 0.09g.(27%). Methyl 2,3,4-tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranoside had $[\alpha]_D +219^\circ$ (c 1.8 in chloroform); m.p. $54-55.5^\circ$. (Found : C, 47.2; H, 5.9; S, 11.6; $C_{12}H_{18}O_7S$ requires C, 47.0; H, 5.9; S, 10.5%).

From the rotation $[\alpha]_D^{+35^\circ}$ (c 1.5 in chloroform), of the crude product from the acetobromo sugar it was calculated that the two anomers were present in the proportion α/β :35/65. In paper chromatography (solvent D, spray c) the two anomers α - and β - had R_F values 0.50 and 0.32 respectively. The R_F value for 2,3,4-tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranosyl 1-bromide, using the same solvent system was 0.42.

(a) Partition chromatography of the methyl α - and β - triacetates.

The methyl α - and β - triacetates could only be partially separated, by partition chromatography on silica gel, using dimethyl sulphoxide as stationary phase⁽¹³⁰⁾.

Silica gel (30g., B.D.H. chromatographic grade) was mixed with dimethyl sulphoxide (DMS) in chloroform (5%v/v; ca. 50 ml.); this suspension was freed from air bubbles in vacuo, then filled into a separating funnel fitted into the top of a chromatographic tube (1 x 50 cm.) containing more of the solvent. The suspension was run into the tube and allowed to settle. The column was washed with at least five column volumes (250 ml.) of an ethyl ether-DMS mixture (1 part dry ether plus 4 parts ethyl ether, which had previously been equilibrated with an excess of DMS containing 4% v/v water), followed by a small quantity of dry ethyl ether and finally with isopropyl ether - DMS mixture (150 ml.),

prepared in the same way as the ethyl ether mixture. The isopropyl ether - DMS mixture was used as eluent. In the washing, when a change of solvent was made, care was taken to prevent the formation of liquid-liquid interfaces.

The crude methyl triacetate mixture (0.3g.) was dissolved in the eluent (1 ml.) and washed onto the column with a further quantity (2 ml.). Elution was carried out and 5 ml. fractions collected. The optical rotation (1 dm. tube) of each fraction was noted (all positive) and each was chromatographed on paper (solvent D, spray c).

<u>Fraction No.</u>	<u>Rotation (α)</u>
1	-
2	-
3	-
4	+ 0.84
5	+ 1.68
6	+ 0.34
7	+ 1.11
8	+ 0.08
9 etc.	-

From the above results and the paper chromatographic evidence, it was obvious that the acetates were not remaining on the column long enough to allow complete separation. Only fraction 4 gave a pure compound, namely,

methyl 2,3,4-tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranoside (0.04g.).

(xiii) Methyl 5-deoxy-5-thio- α -D-xylopyranoside.

5-Deoxy-5-thio- α -D-xylopyranose (2g.) was refluxed with methanolic hydrogen chloride (0.5%; 100 ml.) for six hours. The resulting solution was cooled, neutralised with ion-exchange resin (Amberlite IR 45) and evaporated. The crude mixture, $[\alpha]_D^{+250}$ (c 3.1 in water) was fractionated on a cellulose column (3.5 x 55 cm.) using methyl ethyl ketone/water (10 : 1) as eluent. The main fraction (ca. 95%) was crystallised twice from hot ethyl acetate to give methyl 5-deoxy-5-thio- α -D-xylopyranoside 1.08g. (50%), $[\alpha]_D^{+335}$ (c 0.8 in water); m.p. 113°. (Found : C, 40.3; H, 6.4; S, 17.8. $C_6H_{12}O_4S$ requires C, 40.0; H, 6.7; S, 17.8%). Paper chromatography showed one spot, R_F 0.34 (solvent C, spray a); R_F 0.67 (ethyl acetate/propanol/water - 5:3:2, spray a).

The pure methyl α -glycoside could also be obtained by direct crystallisation of the crude product from hot ethyl acetate.

A faster moving fraction, R_F 0.75 (solvent C, spray a) was also obtained, but could not be crystallised. Tests with dichlorophenol indophenol (cf. p. 50), and with sodium nitroprusside and alcoholic sodium hydroxide, failed to show

the presence of a free -SH group. The faster moving fraction was also tested for the presence of a disulphide with ammoniacal sodium nitroprusside, potassium cyanide and sodium bicarbonate, but the test proved negative. A known disulphide, namely, bis(5-deoxy-D-xylopyranose) 5,5'-disulphide, reacted positively. The compound (or compounds) had a positive rotation, $[\alpha]_D +80^\circ$ (c 2.0 in water), but was not identified.

When the crude reaction product was acetylated (acetic anhydride/pyridine) and run on a chromatogram, a trace of methyl β -triacetate (ca. 1%) was shown to be present indicating that there was a trace of methyl β -glycoside in the original mixture.

(xiv) Methyl 5-deoxy-5-thio- β -D-xylopyranoside and its hemihydrate.

Methyl 2,3,4-tri-O-acetyl-5-deoxy-5-thio- β -D-xylopyranoside (2g.) was dissolved in warm anhydrous methanol (20 ml.) and the resulting solution cooled rapidly to precipitate fine crystals. Sodium methoxide (ca. 1N; 0.8 ml.) was added and the reaction mixture left overnight at 5° . Carbon dioxide was passed through the solution for 30 min. and the solution thereafter concentrated. The residual syrup was taken up in water (20 ml.) and de-ionised (Amberlite resin IR 120 followed by Amberlite resin IR 45). The filtered solution

was concentrated and the resulting product crystallised from methyl alcohol to give methyl 5-deoxy-5-thio- β -D-xylopyranoside, yield : 0.98g.(76%), $[\alpha]_D -72.3^\circ$ (c 2.0 in water); m.p. 160.5-161.5°. (Found : C, 40.1; H, 6.8; S, 19.1. $C_6H_{12}O_4S$ requires C, 40.0; H, 6.7; S, 17.8%).

When the β -glycoside was left in contact with moist air, it was found that it formed a hemi-hydrate $C_6H_{12}O_4S \cdot \frac{1}{2}H_2O$, $[\alpha]_D -67^\circ$ (c 4.4 in water); m.p. 153-160.5°. (Found : C, 38.3; H, 7.2; S, 18.0. $C_6H_{12}O_4S \cdot \frac{1}{2}H_2O$ requires C, 38.2; H, 7.0; S, 17.2%). The following experiment also confirmed the composition of the β -glycoside hemi-hydrate:-

Wt. of β -glycoside (dried in vacuo at 40°)	=	0.03976g.
Wt. of β -glycoside (constant after 3 days in moist air)	=	0.04176g.
Wt. of water taken up	=	0.0020g.
Wt. of water taken up/mol. of glycoside	=	$\frac{0.0020 \times 180}{0.03976}$ g.
	=	9.04g.
	\approx	$\frac{1}{2}$ mol.

(xv) Attempted preparation of the di-acetates of 5-deoxy-1,2-O-isopropylidene-D-xylofuranose 5-thiol.

Both methods of acetylation, namely, using sodium acetate/acetic anhydride (cf. p. 98) and acetic anhydride/pyridine

(cf. p. 99) resulted in an oily product which could not be crystallised, even after one year at 5°.

(xvi) Attempted preparation of the hexa-acetates of bis
(5-deoxy-D-xylofuranose) 5,5'-disulphide.

Both methods of acetate preparation (see above) resulted in an oily product which could not be crystallised.

Section III : Distillation of 5-deoxy-5-thio- α -D-xylopyranose and its oxygen analogue with hydrochloric acid.

(i) Preparation of p-nitrophenylhydrazine reagent.

p-Nitrophenylhydrazine (0.7g.) and aqueous acetic acid (30% v/v; 50 ml.) were boiled for 5 min., allowed to cool overnight and then filtered.

(ii) Quantitative estimation of thiophen-2-aldehyde.

Freshly distilled thiophen-2-aldehyde (0.1417g.) was dissolved in aqueous acetic acid (15% v/v) and the solution made up to 100 ml. with the acetic acid. Three portions (A,B& C; 10 ml. each) of this solution were pipetted into conical flasks (25 ml.), each precipitated with p-nitrophenylhydrazine reagent (3 ml.) and left for 90 min. at room temperature. Each precipitate was filtered through a weighed sintered glass crucible (porosity No. 4), washed thoroughly with water, and dried for an hour at 105°. The precipitate, namely, thiophen-2-aldehyde p-nitrophenylhydrazone had m.p.201°.

Sample	Wt. of p-nitro-phenylhydrazone (g.)	Theoretical Wt. (g.)	% Theoretical
A	0.0320	0.0312	101.5
B	0.0310	"	99.5
C	0.0315	"	101.0

(iii) Quantitative estimation of furfural-2-aldehyde.

Exactly the same technique and procedure were used in the quantitative estimation of furfural-2-aldehyde with p-nitrophenylhydrazine reagent as were used in the estimation of thiophen-2-aldehyde above, and with equally satisfactory results.

(iv) Distillation of 5-deoxy-5-thio- α -D-xylopyranose and its oxygen analogue with hydrochloric acid (12% w/v).

5-Deoxy-5-thio- α -D-xylopyranose (0.0830g.; 0.5 mMol) was weighed into a distillation flask (50 ml.), hydrochloric acid (20 ml., 12% w/v) and a little silicone "anti-foam" (Hopkin and Williams Ltd.) added and the solution brought to the boil in two minutes. The mixture was distilled at a rate of 5 ml./10 min. After a first fraction (5 ml.) had been collected, an additional 5 ml. of acid were added and a second fraction (5 ml.) was collected.

The two fractions were neutralised with sodium hydroxide solution, precipitated with p-nitrophenylhydrazine reagent (4 ml.), allowed to stand overnight, filtered through a weighed sintered glass crucible (porosity No. 4), dried for an hour at 105° and weighed. The results of this experiment are shown in Table 29. The precipitate, namely thiophen-2-aldehyde p-nitrophenylhydrazone had a m.p. 199° and mixed melting-point with a genuine sample (for preparation

see p. 110) 199.5°; recrystallised from absolute ethanol. (Found : C, 53.3; H, 3.8; N, 20.2; S, 13.0. $C_{11}H_9N_3S$ requires C, 53.4; H, 3.7; N, 17.0; S, 13.0%).

The experiment was repeated exactly as detailed above, with α -D-xylopyranose (0.0750 g., 0.5 mMol) instead of the sulphur sugar. The results of this experiment are also shown in Table 29.

Table 29. Distillation of 5-deoxy-5-thio- α -D-xylopyranose and α -D-xylopyranose with hydrochloric acid (12% w/v).

Sugar	Wt. of Reactant (g.)	Wt. of p-nitro-phenylhydrazine		% of reactant reacted (approx.)	
		1st. Fraction	2nd. Fraction		
5-deoxy-5-thio- <u>D</u> -xylopyranose	0.0830	0.0526	0.0126	42	10
<u>D</u> -xylopyranose	0.0750	0.0122	0.0220	10.4	19

Section IV : Miscellaneous.(i) Hydrolysis of methyl 5-deoxy-5-thio- α -D-xylopyranoside with hydrochloric acid (2.0N) at ca. 60°.

Methyl 5-deoxy-5-thio- α -D-xylopyranoside (0.0521g.) was dissolved in hydrochloric acid (5 ml., 2N) at 60° and the reaction mixture contained in a jacketted polarimeter tube (0.5 dm., 5 ml.), thermostated at 60° \pm 1°, was observed polarimetrically. The results are shown in Table 30.

Table 30. Hydrolysis of methyl 5-deoxy-5-thio- α -D-xylopyranoside with hydrochloric acid (2.0N) at ca. 60°.

Time (min.)	Rotation °	Time (min.)	Rotation °
2	+1.70	93	+0.85
14	+1.44	109	+0.81
23	+1.37	154	+0.72
32	+1.25	217	+0.68
41	+1.15	304	+0.61
50	+1.07	369	+0.57
63	+0.98	1245	+0.18
72	+0.92	1434	+0.15
78	+0.89	1799	+0.08
89	+0.85	ca.2880	ca.0.0

After 48 hours, the reaction mixture had become very dark and contained a black precipitate. The mixture was filtered and made up to 25 ml. with water. A 10 ml. portion of the latter solution was precipitated with *p*-nitrophenylhydrazine reagent (5 ml.) and left for one hour at room temperature. The precipitate was filtered through a sintered glass crucible (porosity No. 4), washed with water, dried at 105° and weighed.

Wt. of *p*-nitrophenylhydrazone = 0.0134g.

Theoretical yield of thiophen-2-aldehyde *p*-nitrophenylhydrazone for the 10 ml. aliquot = 0.0286g.

Thiophenaldehyde in reaction mixture after
48 hrs. = 47% of the theoretical

The *p*-nitrophenylhydrazone was shown to be identical to a genuine sample of thiophen-2-aldehyde *p*-nitrophenylhydrazone by infrared spectroscopy and mixed melting point.

(ii) Reaction of 5-deoxy-5-thio-D-xylopyranose with hydrochloric acid (2.0N) at ca. 60°.

5-Deoxy-5-thio- α -D-xylopyranose (0.0418g.) was dissolved in hydrochloric acid (5 ml., 2N) and the reaction mixture, contained in a jacketted polarimeter tube (0.5 dm.) thermostatted at 60°, was observed polarimetrically. The results are shown in Table 31. Unfortunately, the temperature control in this experiment was erratic; the experiment was

Table 31. Reaction of 5-deoxy-5-thio- α -D-xylopyranose with hydrochloric acid (2.0N) at ca. 60°.

Time (min.)	$[\alpha]_D^{60}$ °	Time (min.)	$[\alpha]_D^{60}$ °
2	+196.2	30	+167.5
4	+191.4	135	+157.8
6	+189.0	165	+150.7
10	+177.0	195	+148.3
22	+172.2	290	+136.4

discontinued but not before it had been shown that the rotation of the solution ($[\alpha]_D^{60} +136.4^\circ$) was less than the equilibrium rotation ($[\alpha]_D +178^\circ$) for the mutarotation of 5-deoxy-5-thio- α -D-xylopyranose.

(iii) Attempted estimation of methanol with chromotropic acid in the presence of thiophen-2-aldehyde⁽¹⁰⁴⁾.

Reagents:-

Phosphoric acid	-	ca. 5%
Sodium bisulphite	-	Saturated solution
Potassium permanganate	-	5% aqueous
Chromotropic acid (sodium salt)	-	0.5% in conc. sulphuric acid

Standard Solutions:-

A - Methyl alcohol	49µg/ml.
B - Thiophenalddehyde	53µg/ml.
C - Methyl alcohol	49µg/ml.
Thiophenalddehyde	53µg/ml.

Method:-

1 Ml. of solutions A,B and C were pipetted into separate standard flasks (10 ml.).# To each flask was added phosphoric acid (3 drops) and potassium permanganate solution (5 drops); The mixture was then left for ten minutes at room temperature, with occasional swirling. Sodium bisulphite solution was added dropwise until the colour of the permanganate was discharged. The flasks were cooled in ice-water, conc. sulphuric acid (4 ml.) and chromotropic acid (4 drops) added dropwise and the flasks placed in a water bath at 100° for 30 min. The solutions were cooled to room temperature, made up to the mark with concentrated sulphuric acid and shaken well. Each solution was measured spectrophotometrically against the blank (580mp; 1 cm. cell). The results are shown in Table 32.

A fourth flask contained water (1 ml.).

Table 32. UV absorbance at 580 m μ .

Solution	Methanol $\mu\text{g/ml.}$	Thiophenalddehyde $\mu\text{g/ml.}$	Absorbance at 580 μ
A	49	-	0.331
	49	-	0.335
B	-	53	0.025
	-	53	0.042
C	49	53	0.488
	49	53	0.480

Section V : Hydrolysis of methyl 5-deoxy-5-thio- α - and β -
D-xylopyranosides and methyl β -D-xylopyranoside :
Estimation of the methanol by Gas-Liquid Chromatography

(i) G.L.C. Apparatus.

A gas chromatography apparatus was designed and assembled with the help of Dr. John Knox of this Department. On page 119 (Fig. III) is a schematic representation of the apparatus, which consisted, essentially, of the following components :

- 1 Flame ionisation detector, made in the Department and provided by Dr. John Knox.

- 1 Perkin-Elmer amplifier (451 - 0170)
- 1 Honeywell-Brown 1mV potentiometric recorder
(Chart speed : 30 ins./hr.)
- 2 Edwards needle valves
- 1 Sample volatilisation chamber (cf. Fig. IV, p. 119)
- 3 Gas cylinders (Hydrogen, Nitrogen, Air) with pressure control heads.
- 1 Adkins (Leicester) thermistor temperature controller. This controller is manufactured for use with a heated sample compartment for the Unicam SP500 Spectrophotometer. After slight modification in the wiring it could be used in conjunction with an appropriate thermistor (S.T.C. Type G14) to control the temperature of the G.L.C. column.
- 1 Column heating jacket, (a glass tube wound with resistance wire) surrounded by another glass tube, insulated with a glass fibre jacket.
- 1 Pyrex U-tube 4mm(internal) x 160 cm. (total length)

(ii) Preparation of G.L.C. Column

A solution of polyethylene glycol 400 (B.D.H. reagent; 1g.) in methylene chloride was added to celite (60/80 mesh; 5g.). The methylene chloride was then evaporated off in vacuo while the mixture was being swirled. The celite/polyethylene glycol preparation was left overnight in vacuo. The prepared celite was poured into the U-tube and packed firmly by vibrating the sides with a ruler and by tapping

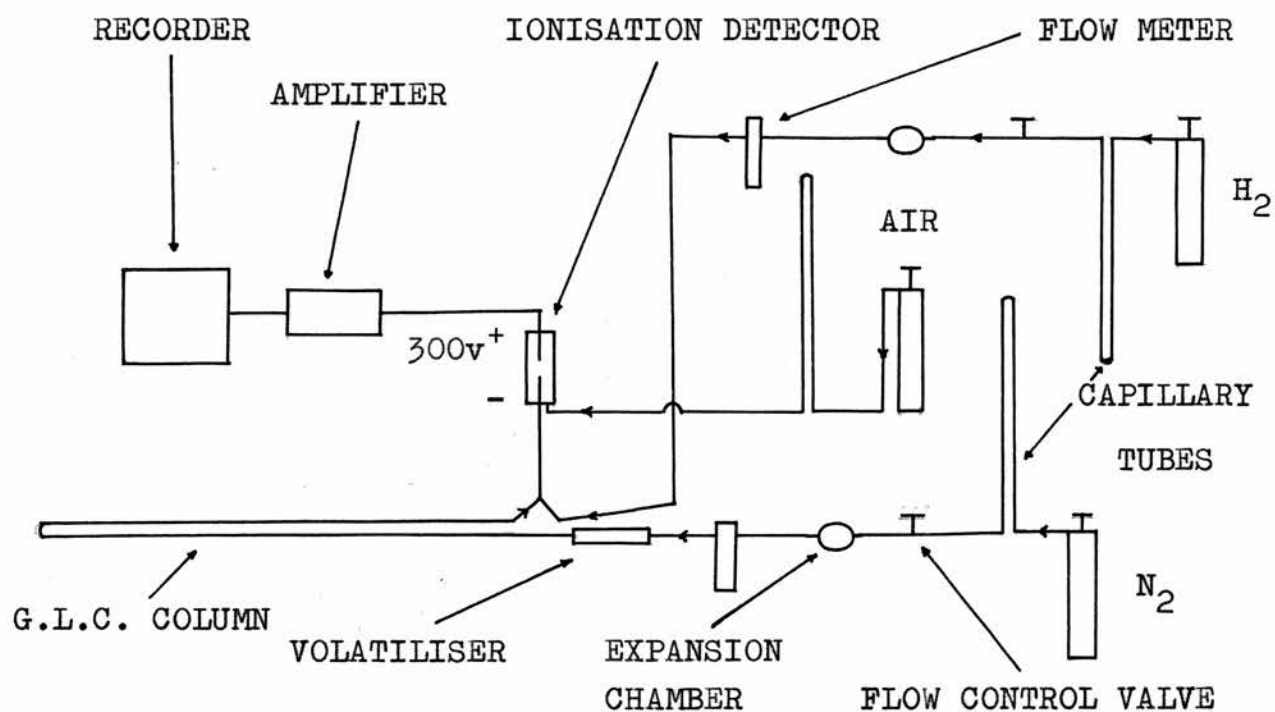


Fig. III

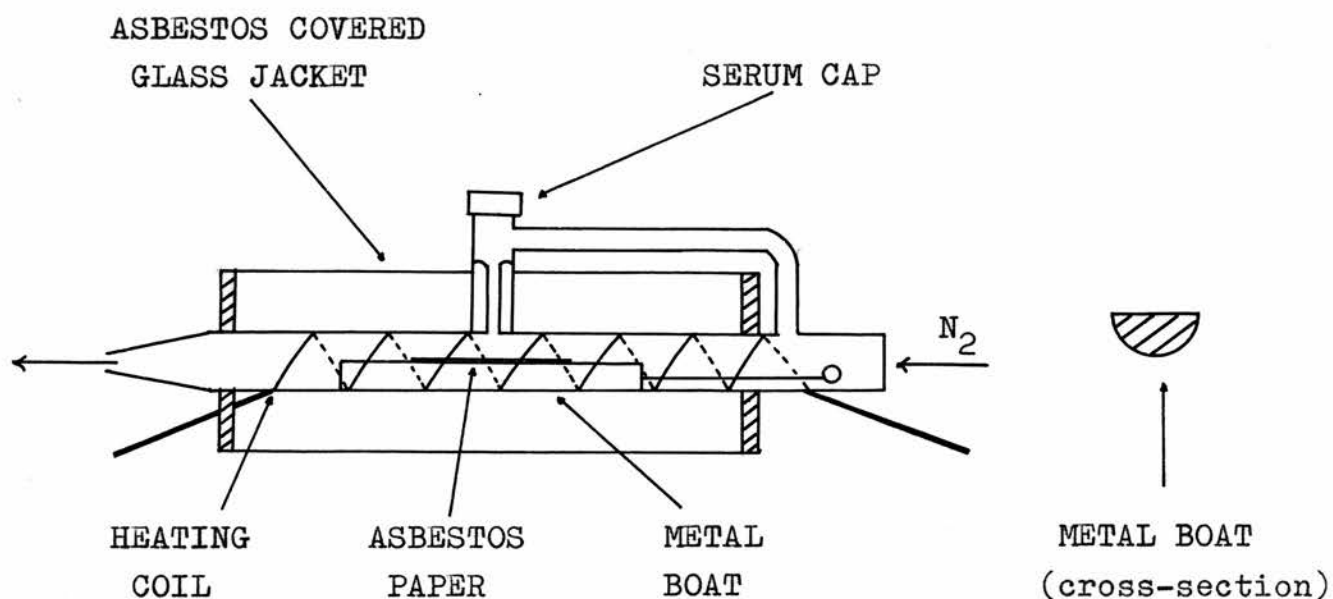


Fig. IV

(ca. Life Size)

the tube on the floor. The final 10 cm. of the exit side of the column was filled with celite/silicone grease, prepared in the same way and in the same proportions as the celite/polyethylene glycol. The ends of the column were plugged with a small piece of cotton wool. The column, resting on cork supports, was maintained at $103^{\circ} \pm 0.2^{\circ}$ inside the insulated column heater.

(iii) G.L.C. Volatilisation Chamber.

Fig. IV shows how the volatilisation chamber was constructed. The serum cap was changed when necessary, as was the thin asbestos-paper (which served to spread out the injected sample and give quick volatilisation) on top of the "half-cylinder" metal boat, which fitted inside the volatilisation chamber. The volatilisation chamber was maintained at a temperature of $140-150^{\circ}$.

(iv) G.L.C. Injections.

The samples for analysis (ca. 0.003 ml.) were injected, using an Agla microsyringe, through the serum cap onto the asbestos paper in the volatilisation chamber. The hypodermic needle was tapped gently on the boat after the injection and withdrawn into the cold part of the chamber for 30 sec. before being completely removed. In order to obtain results reproducible to within 1%, we found that the asbestos-paper was essential.

(v) Gas flow-rates.

Hydrogen - ca. 21 mls./min., but constant to 1%

Nitrogen - ca. 15 mls./min., but constant to 1%

Air - ca. 800 mls./min.

(vi) Estimation of methyl alcohol by Gas-Liquid Chromatography.

(a) Solutions - Two master solutions A and B were prepared:-

Soln. A - Solutions of n-propyl alcohol (Fluka PURISS.,
ca. 1.5 ml./litre)

Soln. B - Solution of methyl alcohol (Analar, ca. 1ml./litre)

The methanol content of this solution was
determined volumetrically by oxidation with
standard potassium dichromate (cf. p. 128),
and found to be 881.2 p.p.m. (parts per million).

From these two master solutions were prepared four
standard solutions, 1,2,3 and 4.

Std. Soln No.	Master Soln. B (ml.)	Master Soln. A (ml.)	Water (ml.)	Total vol. (ml.)	Methanol (p.p.m.)
1	50	25	25	100	440.6
2	40	25	35	100	352.4
3	20	25	55	100	176.2
4	10	25	65	100	88.1

Each solution contained the same quantity of n-propyl alcohol with a known weight of methyl alcohol.

(b) Preliminary experiments.

The aim of the preliminary experiments was to perfect a method for analysing solutions of methyl alcohol by G.L.C. with 1% reproducibility. The preliminary experiments were carried out on a solution similar to standard solution No. 1. While we were carrying out these experiments, we bore in mind that the method was eventually to be used to follow the hydrolysis of a methyl glycoside. The preliminary experiments included variation of :-

- (a) the grade of polyethylene glycol used
- (b) the flow-rates of the gases
- (c) the volume and technique of sample injection
- (d) the design of the volatiliser
- (e) the temperature control of the column
- (f) the recording and measurement of the peak heights of the separated propanol and methanol.

A considerable amount of work was required before the conditions described here were finally evolved.

(c) Procedure.

The microsyringe was washed out with water and a sample of standard No. 1 drawn in, ejected, and a fresh sample drawn in. A sample (ca. 0.003 ml.) of this solution was then

injected into the volatilisation chamber in the prescribed manner. Each analysis took about four minutes from the time of injection until the final (propanol) peak had been recorded; an interval of a further twelve minutes was found advisable, to allow column conditions to stabilise, before a second sample was injected. The peak heights of the methanol and propanol peaks were measured as in Fig. V, and the ratio:-

Height of methanol peak

Height of propanol peak

calculated. Normally the second and third injections gave the required reproducibility for the methanol/propanol peak height ratio (within 1% of each other), but the first injection of a series was always rejected. Between samples of different methanol content it was only necessary to wash out the syringe with distilled water; as each sample had its own "built in" propanol standard there was no need to dry the syringe. The analysis of samples was carried out in the following order:-

<u>Injection No.</u>	<u>Sample injected</u>		
1	Standard No.1	rejected	
2	Standard No.1	<u>methanol</u> propanol	within 1% of each other
3	Standard No.1		
4	Sample No.1	<u>methanol</u> propanol	within 1% of each other
5	Sample No.1		

continued:

<u>Injection No.</u>	<u>Sample injected</u>	
6	Standard No.1	
7	Sample No.2	<u>methanol</u> within 1% of <u>propanol</u> each other
8	Sample No.2	
9	Standard No.1	
10	etc.	

(d) Calculation of the methanol content.

Master solution B was analysed volumetrically (cf. p.128) and found to contain 88lp.p.m. of methyl alcohol, therefore standard solution No.1 (cf. p.121) contained 440.5p.p.m. of methanol. As all the standard solutions contained the same quantity (albeit unknown) of propyl alcohol, the ratio of the methanol/propanol peak heights of the solutions could be compared directly with the ratio obtained for the standard solution No.1, and their G.L.C. methanol content calculated from the formula:-

$$\text{Methanol (p.p.m.)} = \frac{R_s \times M_{st}}{R_{st}}$$

$$\text{where } R_s = \frac{\text{Methanol Peak Ht.}}{\text{Propanol Peak Ht.}} \quad \text{of Sample}$$

$$M_{st} = \text{Methanol content of Standard No.1}$$

$$R_{st} = \frac{\text{Methanol Peak Ht.}}{\text{Propanol Peak Ht.}} \quad \text{of Standard No.1}$$

$$= (\text{average})$$

Peak heights:- Methanol = 74.9 - 5.8 = 69.1
 n-Propanol = 62.6 - 7.0 = 55.6

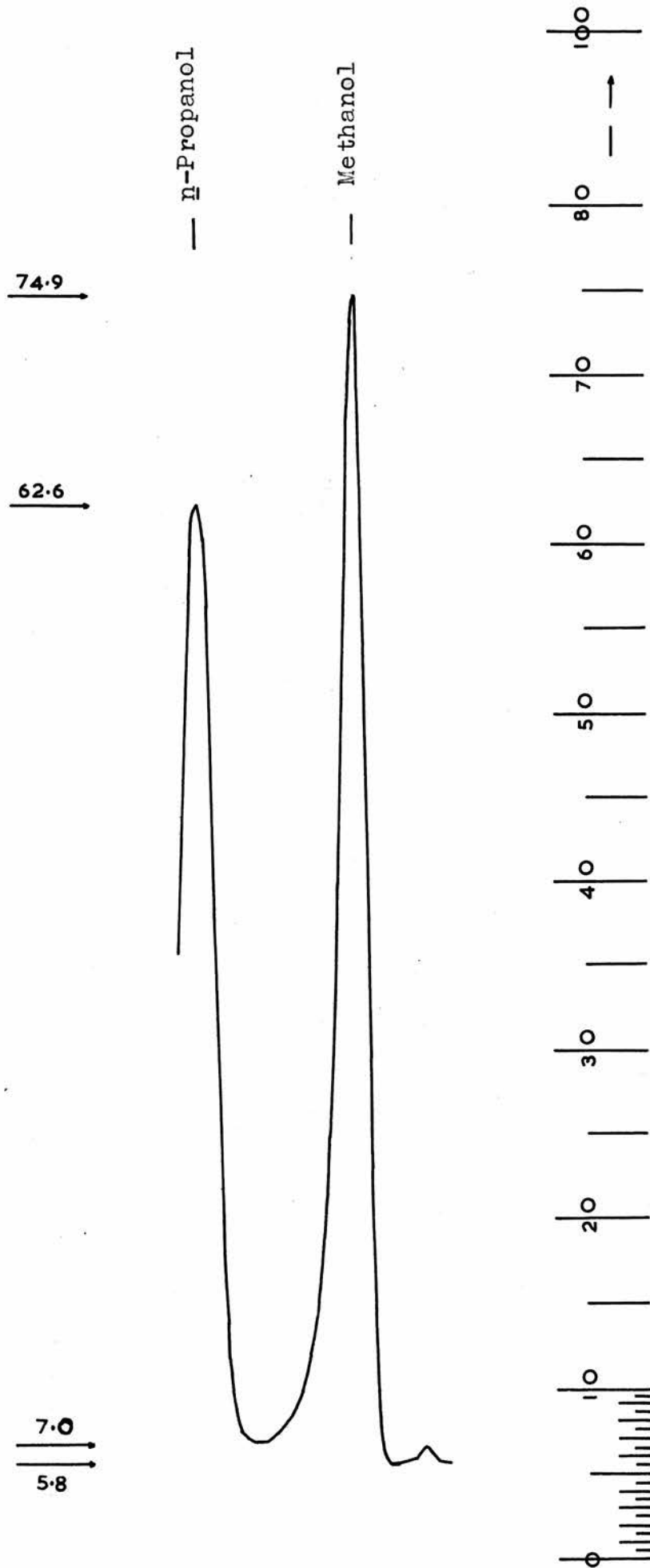


Fig. V.

e.g. From Table 33, we see from the results of injections 5 and 8, that the average peak height ratio:-

$$R_{st} = \frac{1.279 + 1.276}{2} = 1.278$$

and this figure is used to calculate the G.L.C. methanol content of injections 6 and 7. Thus for injection 6 (i.e. Standard soln. No.2):-

$$\begin{aligned} \text{Methanol (p.p.m.)} &= \frac{1.023 \times 440.6}{1.278} \\ &= 352.8 \end{aligned}$$

(e) Linearity of the G.L.C. results.

The four standard solutions Nos. 1,2,3 and 4 were used to ascertain that the ratio:-

$$\frac{\text{Peak height of methanol}}{\text{Peak height of propanol}}$$

was a linear function of the methanol content, over the range 80-450p.p.m. of methanol against a constant propanol content. The results are shown in Table 33.

(f) Stability of a methanol/propanol standard solution to hydrochloric acid (0.2N).

A standard solution (Stability solution X), 0.2N with respect to hydrochloric acid and containing 220.3p.p.m. of methyl alcohol, was prepared as follows:-

Table 33. G.L.C. analysis of (a) Standard solns. Nos.1,2, 3 & 4 and (b) Stability solution X.

Injection	Solution Injected	Meth./Prop. Peak ht. ratio	Methanol by G.L.C. p.p.m.	Methanol by titration p.p.m.	
A.	1	Std. No.1	1.274	-	440.6
	2	Std. No.1	1.275	-	440.6
	3	Std. No.1	1.277	-	440.6
	4	Std. No.1	1.276	-	440.6
	5	Std. No.1	1.279	-	440.6
	6	Std. No.2	1.023	352.8	352.4
	7	Std. No.2	1.021	352.1	352.4
	8	Std. No.1	1.276	-	440.6
	9	Std. No.3	0.511	176.5	176.2
	10	Std. No.3	0.510	176.2	176.2
	11	Std. No.1	1.275	-	440.6
	12	Std. No.4	0.255	87.8	88.1
	13	Std. No.4	0.257	88.5	88.1
	14	Std. No.1	1.285	-	440.6
B.	1	Std. No.1	1.264	-	440.6
	2	Std. No.1	1.270	-	440.6
	3	Stability Soln. X	0.634	221.0	220.3
	4	"	0.636	220.6	220.3
	5	Std. No.1	1.270	-	440.6

Master solution A - 12.5 ml.

Master solution B - 12.5 ml.

Hydrochloric acid (0.4N) - 25 ml.

Samples of this solution were sealed in ampoules and maintained at 80° for three days, after which they were cooled, opened, made slightly alkaline with sodium hydroxide solution (2N) and the excess sodium hydroxide neutralised by bubbling carbon dioxide through the solution. The solution was then analysed by G.L.C. and compared with Standard solution No.1. The G.L.C. results are recorded in Table 33.

(vii) Determination of methyl alcohol by standard potassium dichromate⁽¹³¹⁾.

Reagents:

1. Methyl alcohol (ca. 1ml./litre) i.e. Master solution B.
2. 0.1N Potassium dichromate/nitric acid solution. 3 Parts by volume of nitric acid (S.G. 1.31) were diluted with 1 part of distilled water and blown with nitrogen until free from nitrous vapours. Exactly 4.904g. of potassium dichromate were dissolved in 1 litre of this acid.
3. Sodium thiosulphate (0.1N) solution - 25g. of sodium thiosulphate ($5H_2O$) were dissolved in distilled water, diluted to 1 litre and standardised against the potassium dichromate/nitric acid solution.

4. Potassium iodide - 50g. of potassium iodide/litre
5. Starch indicator solution

Procedure:

Methyl alcohol solution (10 ml.) was pipetted into an Erlenmeyer flask containing 25 ml. of the 0.1N potassium dichromate/nitric acid solution. The flask was stoppered and allowed to stand in a boiling water bath for 10 min. The contents of the flask were diluted with distilled water, potassium iodide solution (5 ml.) added with swirling and the mixture titrated with standard sodium thiosulphate solution, adding starch indicator near the end-point. The end-point is a pale-blue colour; a colourless solution is not obtained.

Methanol content = $(25 - A.F.) \times 0.0533\text{g./litre}$

where A = mls. of sodium thiosulphate used to titrate the excess dichromate.

and F = sodium thiosulphate factor

e.g. Master solution B contained 0.8845g. of methanol by direct weighing (i.e. 885 p.p.m.)

By titration:-

Titration of sodium thiosulphate (0.1024N)

= (a) 8.28 ml. (b) 8.26 ml.

Methanol content of solution B

= (a) $(25 - 8.28 \times 1.024) \times 0.0533 \text{ g./litre}$

(b) $(25 - 8.26 \times 1.024) \times 0.0533 \text{ g./litre}$

= (a) 0.8805g./litre (b) 0.8816g./litre
 = 881 p.p.m. (average in parts per million)

The amount of methanol (Analar reagent) by weight is in good agreement with the amount found by analysis.

(viii) Hydrolysis of the Glycosides.

The hydrolyses of methyl 5-deoxy-5-thio- α - and β -D-xylopyranosides and methyl β -D-xylopyranoside in hydrochloric acid (0.2N) at various temperatures were all carried out using the same technique and method of analysis. The kinetic results have already been recorded in Table 26, but a typical hydrolysis, namely, that of methyl 5-deoxy-5-thio- α -D-xylopyranoside at 60°, is recorded below in detail.

Hydrolysis of methyl 5-deoxy-5-thio- α -D-xylopyranoside at 60° in hydrochloric acid (0.2N).

Hydrolysis solution H was prepared as follows:-

Master solution A - 10 ml.

Hydrochloric acid (0.4N) - 10 ml.

giving a solution 0.2N with respect to hydrochloric acid.

Methyl 5-deoxy-5-thio- α -D-xylopyranoside (0.04084g.) was weighed into a conical flask (10ml.) and the hydrolysis solution H (0.2N, 4 ml.) was added. The flask was cooled in ice-water and swirled until all the glycoside had dissolved. The reaction mixture was then transferred to a graduated syringe, samples (ca. 0.3 ml.) injected into ten ampoules

(ca. 0.6 ml.), and the ampoules carefully sealed. The ampoules were placed in a wire basket, which was immersed in an oil-bath maintained at 60° ($\pm 0.1^{\circ}$); about two minutes after this operation had been completed, a clock was started. #

After 155 minutes an ampoule was withdrawn, quickly cooled in ice-water, wiped clean, opened, and the contents transferred by means of a syringe to a test-tube (1 ml.) containing sodium hydroxide solution (0.2N; 0.3 ml.). After pH paper had shown that the mixture was alkaline, the excess alkali was neutralised by bubbling carbon dioxide (obtained from solid carbon dioxide) through the solution. The last process was found necessary in order that duplicate G.L.C. analysis results be obtained.

Six other ampoules were withdrawn and similarly treated at regular intervals covering the first half-life of the reaction. An eighth ampoule was withdrawn after two half-lives, and a ninth ampoule, withdrawn after ten half-lives,

In a preliminary experiment a thermocouple was inserted, via a serum cap, into an ampoule and the ampoule immersed in an oil-bath maintained at 70° . The contents of the ampoule reached a temperature of 66.6° after 1 minute, 69.6° after 2 minutes, and 70° after 3 minutes.

gave the infinity value of the reaction. The neutralised samples were kept in their stoppered tubes at 5° until they were analysed.

The samples were analysed for methanol content by G.L.C. using the method already described. The methanol content of each sample was calculated from the formula:-

$$\text{Methanol content } m_t = \frac{R_s \times M_{st}}{R_{st}} \times 2 \text{ (p.p.m.)}$$

(for definition of R_s , M_{st} and R_{st} see p. 124, for m_t see below). In this case the factor 2 is necessary, because the hydrolysis solution H (cf. p. 130) contains twice the quantity of n-propyl alcohol, as standard solution No.1 does (cf. p. 121). The results of the G.L.C. analyses are recorded in Table 34.

The first-order rate constants for all the glycoside hydrolyses were obtained (using the results of the first half-life) from the slope of the plot, $\log(m_\infty - m_t)$ against t , where m_t is the methanol liberated after time t , and m is the final methanol content, as calculated from the amount weighed out. In all the experiments, m_t , after > 10 half-lives, was within 1% of the methanol content (m_∞) expected from the quantity of glycoside used. Good first-order plots were obtained.

The graph (a typical one) of the results of the above experiment is shown on page 133a.

Table 34. Hydrolysis of methyl 5-deoxy-5-thio- α -D-xylopyranoside in hydrochloric acid (0.2N) at 60°.

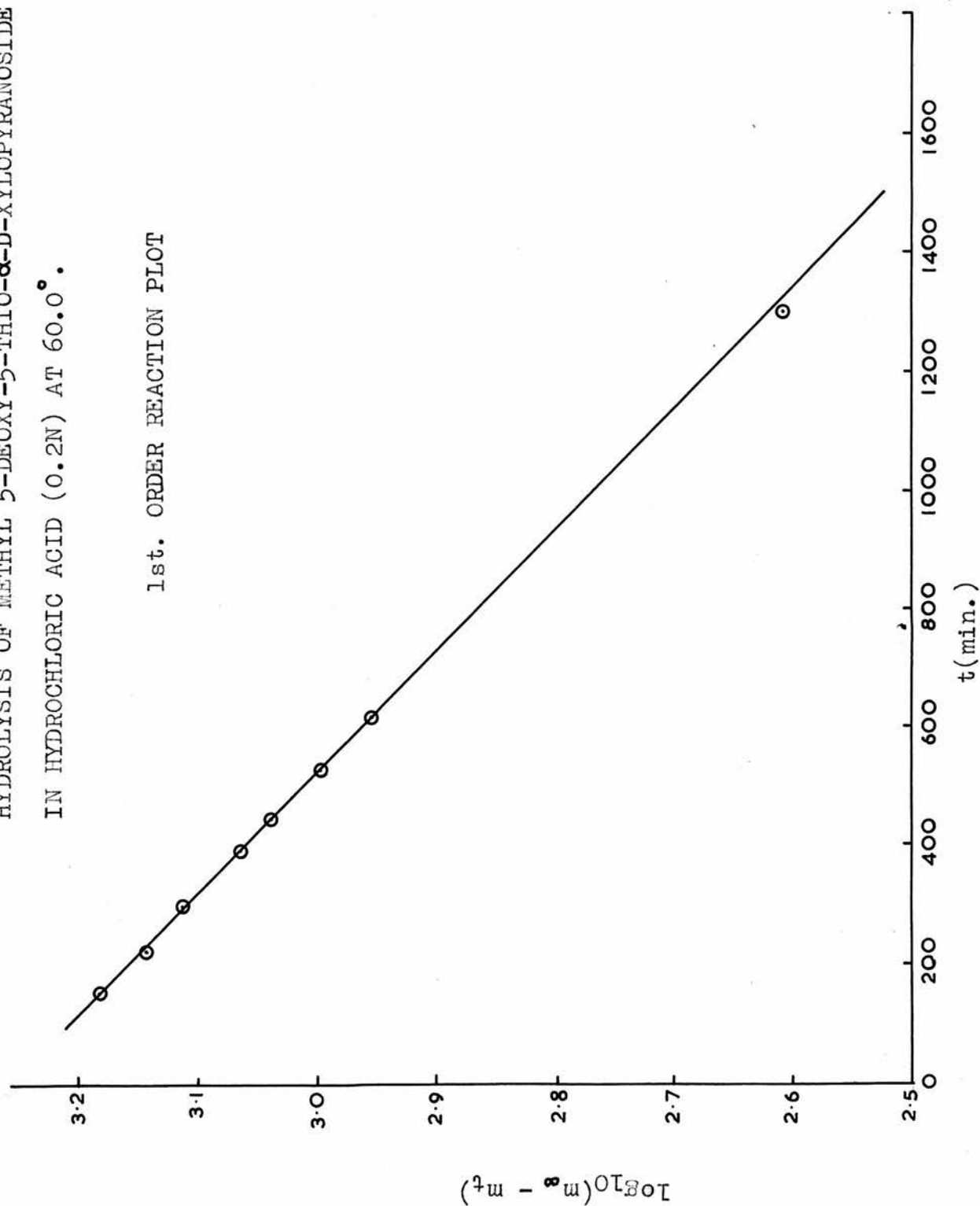
Ampoule No.	Time (min.)	R _s	R _{st}	m _t # (p.p.m.)	m _∞ - m _t	log ₁₀ m _∞ - m _t
1	155	0.350	1.214	291	1524	3.1829
		0.350	1.213			
2	225	0.502	1.206	419	1396	3.1449
		0.500	1.206			
3	295	0.609	1.206	510	1305	3.1155
		0.604	1.195			
4	390	0.771	1.195	653	1162	3.0652
		0.774	1.195			
5	446	0.851	1.195	718	1097	3.0402
		0.851	1.195			
6	525	0.968	1.198	815	1000	3.0000
		0.961	1.192			
7	615	1.058	1.172	911	904	2.9562
		1.054	1.168			
8	1300	1.634	1.168	1408	407	2.6096
		1.646	1.179			
9	>4 days	2.112	1.179	1808	7	-
		2.124	1.183	(1815) [‡]		

M_{st} in this case = 504p.p.m.

‡ m_∞ is calculated from the amount of glycoside taken

HYDROLYSIS OF METHYL 5-DEOXY-5-THIO- α -D-XYLOPYRANOSIDE
IN HYDROCHLORIC ACID (0.2N) AT 60.0°.

1st. ORDER REACTION PLOT



Section VI : Methanolysis of 2,3,4-tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranosyl 1-bromide and its oxygen analogue.

(i) Apparatus

The methanolysis was carried out in a thermostatted glass polarimeter cell (20mm.) and the progress of the reaction followed polarimetrically on an N.P.L.-E.T.L. photoelectric polarimeter (Bendix-Ericsson, Ltd., Nottingham) coupled to a Honeywell-Brown 10mV potentiometric recorder. The sensitivity and zero of the polarimeter were set previous to the commencement of the experiment, such that the progress of the whole reaction could be followed as accurately as possible i.e. using practically the full scale of the recorder. These adjustments required a knowledge of the change of rotation occurring during the reaction for a given concentration of reactant; this change in rotation was determined by a preliminary experiment.

(ii) Temperature control

The contents of the polarimeter cell were kept at a constant temperature by circulating water from a thermostat bath, through a jacket surrounding the cell. The apparatus was run in a room, the temperature of which was controlled at $22^{\circ} \pm 1^{\circ}$. Preliminary experiments, involving the insertion of a thermocouple into the cell and thermostat bath, ascertained

that the temperature of the contents of the cell was between 0.1° and 0.2° below that of the bath. Thus, from a knowledge of the temperature of the bath, we were always able to calculate the temperature of the contents of the cell.

(iii) Experimental technique

Methanol (10 ml., anhydrous) was pipetted into a conical flask (25 ml.) and the stoppered flask immersed for about one hour in the thermostatted water bath. A powdered sample of the acetohalo sugar was then introduced into the flask (the weight of this sample was obtained by difference) and the contents mixed thoroughly. Using a hypodermic syringe (which was kept in a tube immersed in the bath before use), a portion of the reaction solution was rapidly transferred to the polarimeter cell, and the cell inserted in the polarimeter. The complete operation took about three minutes.

The progress of the reaction was recorded continuously on the chart of the recorder. The chart speed was adjusted to suit the particular duration of reaction and it was adjusted to a slower speed after three half-lives, if the reaction-time was particularly long.

Weight of 2,3,4-tri-O-acetyl- α -D-xylopyranosyl 1-bromide used:- 27 mg. accurately weighed; a 6 ohm external resistance was used. Weight of 2,3,4-tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranosyl 1-bromide used :- ca. 30mg. accurately weighed; a 6ohm external resistance was used. Initial $[\alpha]_D +240^{\circ}$;

final $[\alpha]_D$ ca. $+130^\circ$.

(iv) Kinetic results

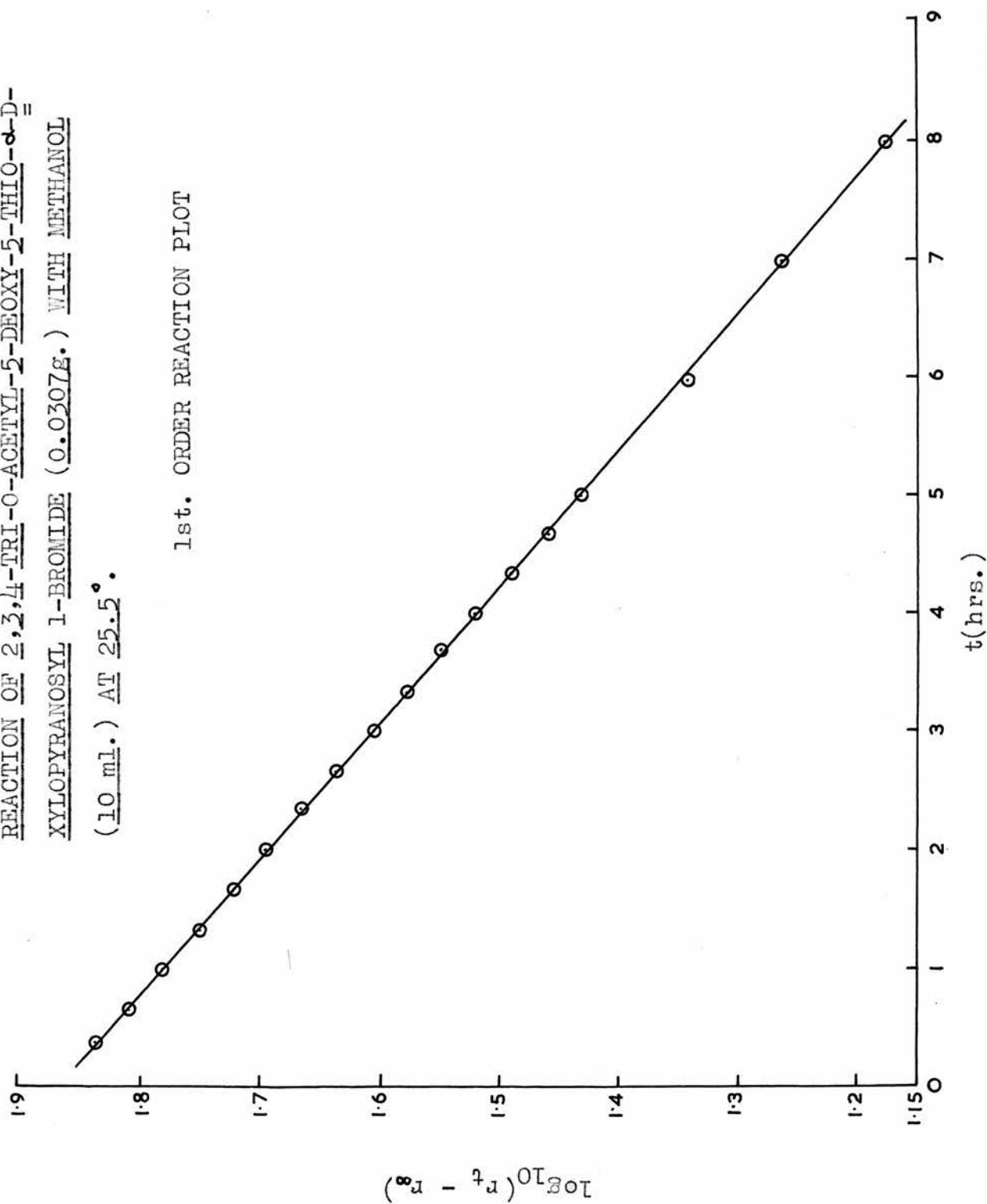
The kinetic results of the methanolysis of the two acetohalo-sugars have already been recorded in Table 25 (p.68); however the complete results for a typical run are shown in Table 35. The first-order rate constants for the reactions were calculated from the slope of the plot, $\log(r_t - r_\infty)$ against t , where r_t is the recorder reading at time t , and r_∞ is the reading at t_∞ (>10 half-lives). The plot of the results of the above reaction (cf. Table 35) is shown on page 138. In the case of the methanolysis of the xylopyranosyl bromide, the rate constant was obtained from the results of the first four half-lives. Paper chromatography (Solvent D, spray c) showed that even after ten half-lives, deacetylation was only very slight. In calculating the rate constant for the corresponding reaction with the sulphur sugar, results obtained in the first two half-lives only were used. Thin layer chromatography (silica gel; ethyl acetate/benzene : 3/7) showed that deacetylation was only slight at three half-lives but thereafter it became progressively greater. After ten half-lives the product of the reaction, as ascertained by paper chromatography, was mainly deacetylated material ($>90\%$), including methyl 5-deoxy-5-thio-D-xylopyranosides ($>50\%$).

Table 35. Reaction of 2,3,4-tri-O-acetyl-5-deoxy-5-thio- α -D-xylopyranosyl 1-bromide (0.0307g.) with methanol (10 ml.) at 25.5°.

Time t (hrs.)	Recorder reading r_t	\log_{10} ($r_t - r_\infty$)	Time t (hrs.)	Recorder reading r_t	\log_{10} ($r_t - r_\infty$)
0.33	81.2	1.840	9	24.5	1.097
0.66	76.9	1.812	10	22.5	1.021
1.00	72.6	1.783	11	20.8	0.945
1.33	68.7	1.754	12	19.5	0.875
1.66	65.0	1.724	13	18.5	0.813
2.00	61.6	1.696	14	17.5	0.740
2.33	58.5	1.668	16	16.2	0.623
2.66	55.4	1.638	18	15.0	0.477
3.00	52.5	1.608	20	14.6	0.415
3.33	50.0	1.580	22	14.1	0.322
3.66	47.5	1.550	24	13.8	0.255
4.00	45.2	1.521	26	13.5	0.176
4.33	43.0	1.491	28	13.1	0.041
4.66	41.0	1.462	30	13.0	0.000
5.00	39.1	1.433	32	12.8	1.903
6.00	34.1	1.344	36	12.5	1.699
7.00	30.3	1.263	40 (∞)	12.0 r_∞	-
8.00	27.0	1.176			

REACTION OF 2,3,4-TRI-O-ACETYL-5-DEOXY-5-THIO- α -D-XYLOPYRANOSYL 1-BROMIDE (0.0307g.) WITH METHANOL
(10 ml.) AT 25.5°.

1st. ORDER REACTION PLOT



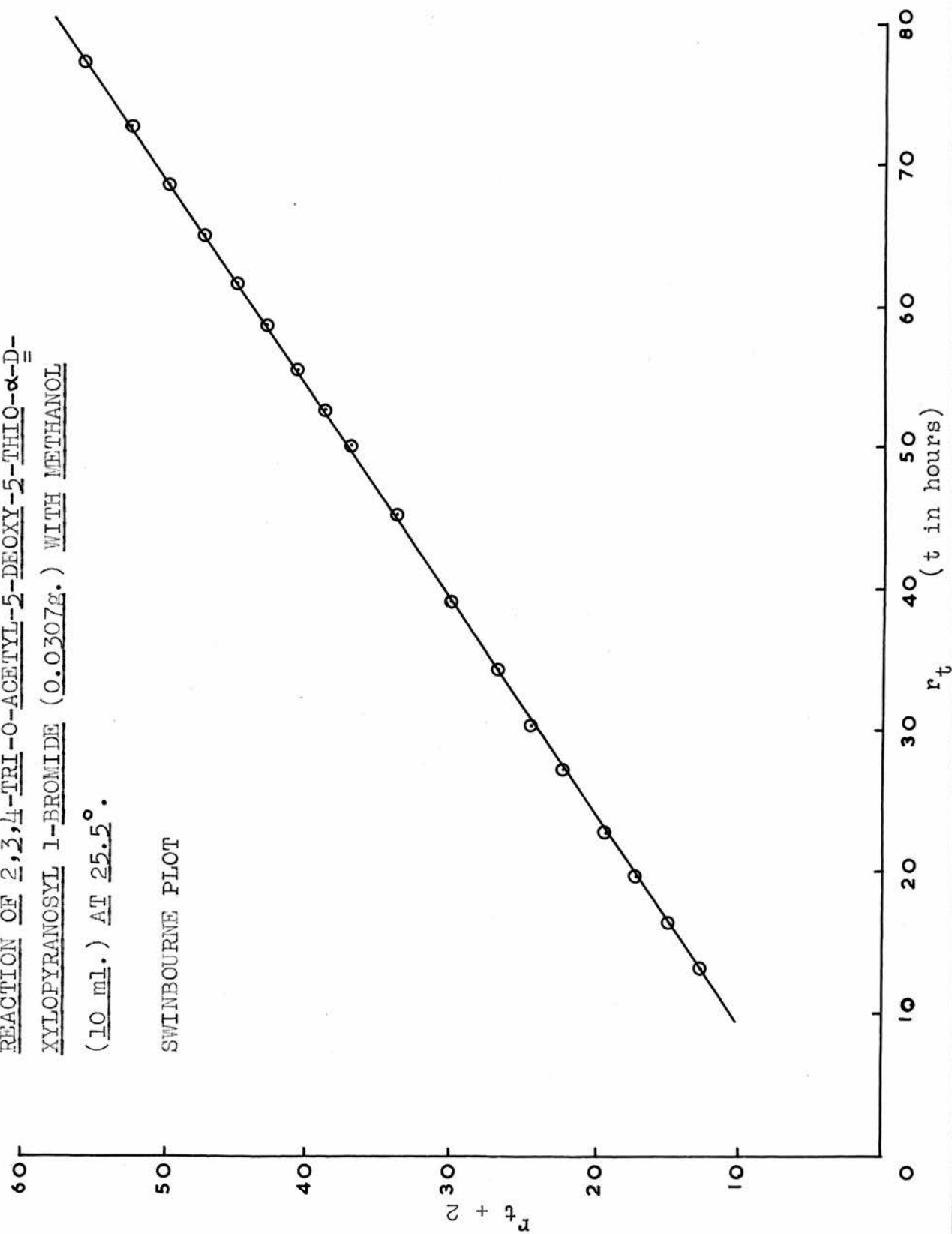
After ten-half-lives the reaction mixture of the latter methanolysis was neutralised (Amberlite resin, IR45), the methanol evaporated off and the residue acetylated with acetic anhydride/pyridine. Paper chromatography (Solvent D, spray c) of the acetylated product showed that the methyl α -triacetate and the methyl β -triacetate were present in the ratio of about 10 : 1.

Because of the excessively large amount of deacetylation in the methanolysis of the sulphur sugar bromide, a value for the rate constant for the reaction was calculated by the method of Swinbourne⁽⁹⁸⁾. The two values were in good agreement (cf. p.68). The Swinbourne plot of the results of the above reaction (cf. Table 35) is shown on page 140. In the Swinbourne method, pairs of recorder readings (r_t ; $r_t + \Delta t$) which were separated by a constant time interval ($t = 2$ hrs.) were plotted against each other. This procedure gave a straight line with a slope related to the rate constant k by the equation:- $k = \frac{1}{\Delta t} \cdot \ln (\text{slope})$

No end-value is needed in this method; however the estimation of the end-value ($r_\infty = 12.4$), by extrapolation of the straight-line Swinbourne plot, was in good agreement with that obtained experimentally ($r_\infty = 12.0$).

REACTION OF 2,3,4-TRI-O-ACETYL-5-DEOXY-5-THIO- α -D-XYLOPYRANOSYL 1-BROMIDE (0.0307g.) WITH METHANOL
(10 ml.) AT 25.5°.

SWINBOURNE PLOT



Section VII : Mutarotation of 5-deoxy-5-thio- α -D-xylopyranose and α -D-xylopyranose.

The apparatus and the technique used to follow the mutarotation of the two sugars were the same as described above (p.134) for the methanolysis of the acetohalo sugars. The weight of sulphur sugar used was ca. 35 mg. and the external resistance was 6 ohms. The weight of D-xylopyranose used was ca. 50 mg. and the external resistance 2 ohms. The results of the mutarotation experiments are tabulated on p.57; in addition the complete results for a typical run are detailed below in Table 36. The buffered solutions A and B, correspond to buffers 6 and 5 respectively, used by Isbell and Pigman⁽⁸³⁾ in their mutarotation experiments. Buffer A - Potassium hydrogen phthalate (0.204g., analar) was dissolved in de-ionised water and made up to 1 litre; pH 4.4.

Buffer B - Sodium hydroxide solution (0.1064N, 45.4 ml.) was added to potassium hydrogen phthalate solution (0.010N; 500ml.) and the solution diluted to one litre with de-ionised water; pH 6.45.

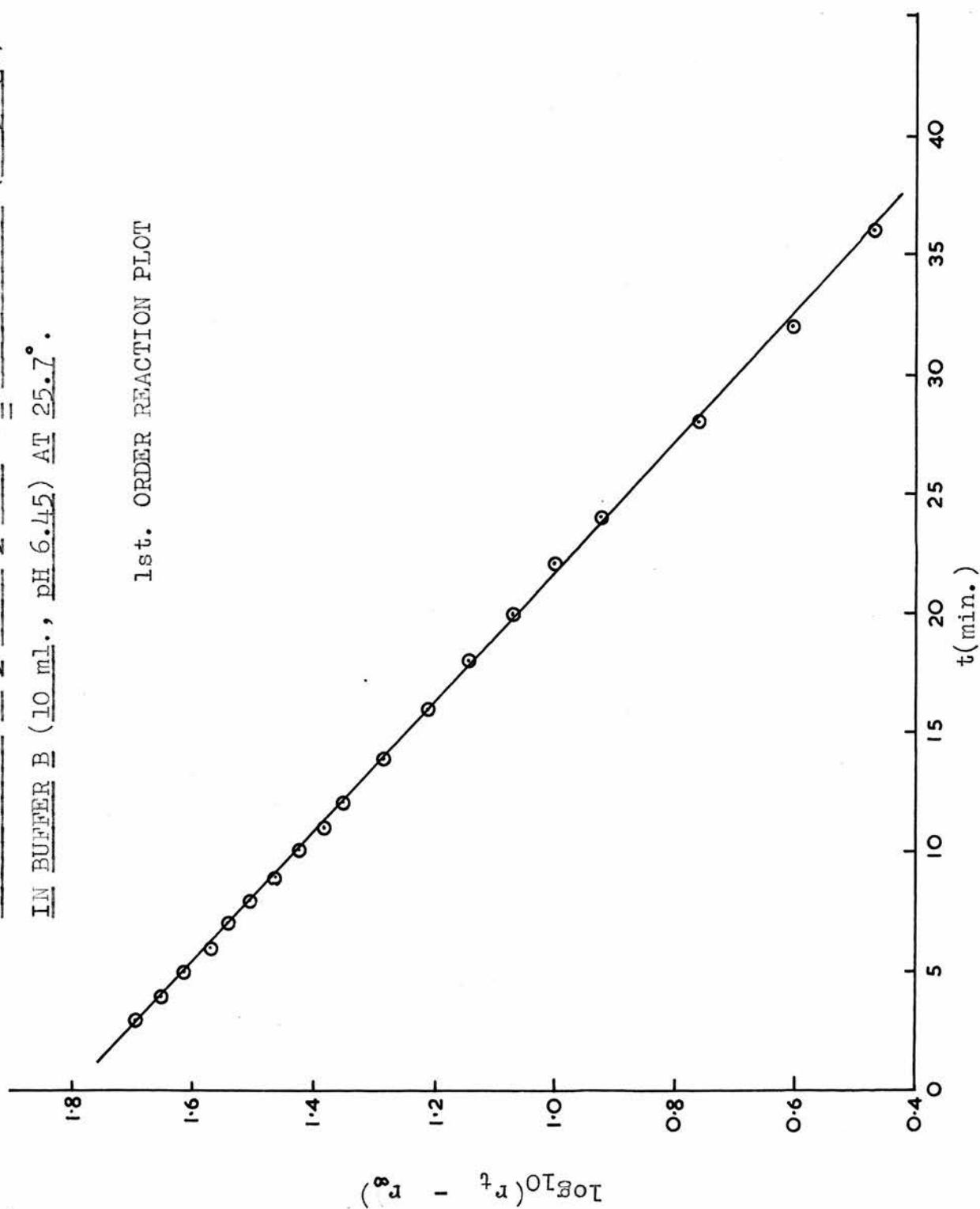
The first-order rate constants were obtained from the slope of the plot, $\log(r_t - r_\infty)$ against t , where r_t is the recorder reading at time t , and r_∞ is the reading after >10 half-lives. The plot of the results of the above reaction (cf. Table 36) is shown on page 143.

Table 36 : Mutarotation of 5-deoxy-5-thio- α -D-xylopyranose
(0.0360g.) in Buffer B (10 ml., pH 6.45) at 25.7°.

Time t (mins.)	Recorder reading r_t	\log_{10} ($r_t - r_\infty$)	Time t (mins.)	Recorder reading r_t	\log_{10} ($r_t - r_\infty$)
3	93.5	1.699	22	53.6	1.004
4	89.0	1.658	24	52.0	0.929
5	85.0	1.618	28	49.3	0.763
6	81.4	1.579	32	47.5	0.602
7	78.5	1.544	36	46.4	0.462
8	75.7	1.508	40	45.5	0.301
9	73.0	1.470	44	45.0	0.176
10	70.5	1.431	48	44.5	0.000
11	68.0	1.389	52	44.4	I-954
12	66.2	1.356	56	44.1	I.778
14	62.9	1.288	60	44.0	I.699
16	59.9	1.215	70	43.9	I.602
18	57.5	1.146	80 (∞)	43.5 (r_∞)	-
20	55.3	1.072			

MUTAROTATION OF 5-DEOXY-5-THIO- α -D-XYLOPYRANOSE (0.0360g.)
 IN BUFFER B (10 ml., pH 6.45) AT 25.7°.

1st. ORDER REACTION PLOT



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